WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Thursday, May 03, 2007

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L51	L50 and UCDA	0
☐	L50	L48 and (liver)adj(cirrhosis)	132
☐	L49	L48 and (liver)adj(cirosis)	0
☐	L48	L47 and (heart)adj(failure)	166
☐	L47	L46 and TNF	181
☐	L46	L45 and diuretics	252
☐	L45	L44 and combination	1335
☐	L44	L43 and (ursodeoxycholic)adj(acid)	1517
☐	L43	treatment	2242251
☐	L42	L41 and (treating)adj(endotoxin)adj(mediated)adj(TNF)adj(production)	0
☐	L41	L40 and cachexia	161
☐	L40	L39 and inflammation	166
☐	L39	L38 and (heart)adj(failure)	166
☐	L38	L37 and treatment	179
☐	L37	L36 and TNF	179
☐	L36	L35 and formulation	255
☐	L35	(ursodeoxycholic)adj(acid)and(diuretics)	280
☐	L34	(ursodeoxycholic)adj(acid)same(diuretic)	29
☐	L33	L32 and (heart)adj(failure)	170
☐	L32	L31 and endotoxin	180
☐	L31	L30 and (ursodeoxycholic)adj(acid)	269
☐	L30	L29 and diuretic	17332
☐	L29	composition	2806036
☐	L28	L27 and (ursodeoxycholic)adj(acid)	7
☐	L27	(424/455).ccls.	546
☐	L26	(schumann)adj(ralf)adj(reiner)	2
☐	L25	(mathias)adj(rauchhaus)	0
☐	L24	(rauchhaus)adj(mathias)	0
☐	L23	(rauchhaous)adj(mathias)	0
☐	L22	(rauchaus)adj(mathias)	0
☐	L21	(volk)adj(hans-dieter)	21

☐	L20	(coats)adj(andrew)	3
☐	L19	(anker)adj(stefan)	4
☐	L18	5674855.pn.	2
☐	L17	5589358.pn.	2
☐	L16	5514696.pn.	2
☐	L15	L12 and diuretic	164
☐	L14	L12 and diuretic	164
☐	L13	L12 and diuretic	164
☐	L12	L11 and (heart)adj(failure)	175
☐	L11	L10 and endotoxin	187
☐	L10	(ursodeoxycholic)adj(acid)same(combination)	336
☐	L9	(ursodeoxycholic)adj(acid)same(combination)same(diuretic)	8
☐	L8	L7 and diuretics	170
☐	L7	L6 and (ursodeoxycholic)adj(acid)	195
☐	L6	L5 and endotoxin	2911
☐	L5	(heart)adj(failure)	33716
	DB=USPT; PLUR=YES; OP=OR		
☐	L4	5514696.pn.	1
☐	L3	5674855.pn.	1
☐	L2	5674855.pn.	1
☐	L1	5589358.pn.	1

END OF SEARCH HISTORY

1: Surg Today. 1997;27(2):140-4.

Protective effect of the intravenous administration of ursodeoxycholic acid against endotoxemia in rats with obstructive jaundice.

Hori Y, **Ohyanagi H**.

Second Department of Surgery, Kinki University School of Medicine, Osaka-Sayama, Japan.

This study was undertaken to elucidate the effect of the intravenous administration of ursodeoxycholic acid (UDCA) on endotoxemia in rats with obstructive jaundice from the viewpoint of the biliary excretion of lipopolysaccharide (LPS) through hepatocytes. In rats with obstructive jaundice, fluorescein isothiocyanate-labeled LPS was administered via the portal vein and then its biliary excretion was examined. A significant increase in the LPS excretion was thus noticed in UDCA-treated rats at a dose of 0.1 micromol/100 g body wt. per min. In place of UDCA, sodium taurocholate at the same dose also enhanced the biliary excretion of LPS. Secondly, we also examined whether or not UDCA protects against endotoxemia. In this experiment, nonlabeled LPS was administered via the portal vein and its peripheral concentration was then measured. In UDCA-treated rats, the endotoxin concentration was significantly lower. Finally, to elucidate the effect of UDCA on Kupffer cells, serum tumor necrosis factor (TNF-alpha) was measured. But UDCA had no effect on the TNF-alpha level. These findings thus demonstrate that the intravenous administration of UDCA protects against endotoxemia by enhancing the transport of LPS across the hepatocytes from blood to bile without affecting Kupffer cells, and that this biliary excretion of LPS is dependent on bile acids.

PMID: 9017991 [PubMed - indexed for MEDLINE]

1: Acta Physiol Scand. 1987 Jul;130(3):447-55.

The effect of amiloride on biliary HCO3- secretion in the anaesthetized pig.

Grotmol T, **Buanes T**, **Raeder MG**.

The present study was performed on 29 anaesthetized pigs and shows that the bile acid ursodeoxycholic acid (UDCA) produces a flow of bile rich in HCO3- compared with taurocholic acid (TCA). The slope relating biliary HCO3- secretion to bile acid secretion was 0.59 (0.44-0.82) and 0.33 (0.29-0.38) during venous infusion of UDCA and TCA, respectively. We next wanted to evaluate the importance of Na+/H+ ion exchange for biliary HCO3- secretion. High doses of amiloride were employed in order to impair the hepatic Na+/H+ ion exchanger. It was reasoned that any reduction in H+ efflux through the hepatic Na+/H+ ion exchanger involved in causing biliary HCO3- secretion would be translated into an equimolar fall in biliary HCO3- secretion. We found that amiloride (2.0 X 10(-4) mol l-1 plasma) reduced UDCA-dependent canalicular HCO3- secretion by 26 (14-35)% without concurrently reducing bile acid secretion. Amiloride (2.9 X 10(-4) mol l-1 plasma) did not significantly reduce secretin-dependent ductular HCO3- secretion. In this group of animals amiloride reduced bile acid secretion by 13 (5-22)%. It is concluded that Na+/H+ ion exchanger is essential for UDCA-dependent canalicular HCO3- secretion, but not for secretin-dependent ductular HCO3- secretion.

PMID: 3630723 [PubMed - indexed for MEDLINE]

ercise, respectively; Table I). These results indicate that BP control at rest with antihypertensive medication alone may not provide adequate protection against excessive rise in BP during physical exertion. However, the addition of aerobic exercise to therapy can prevent excessive elevations of BP during physical exertion even with modest reductions in BP at rest. Thus, hypertensive patients with no evidence of clinically significant contraindications to exercise should be encouraged to engage in regular aerobic exercise of mild to moderate intensity, even when BP at rest is well controlled with medication.

In conclusion, we found that the addition of moderate aerobic exercise to medical antihypertensive therapy in African-American patients with severe hypertension attenuates excessive elevations in BP during physical exertion even with modest reductions in BP at rest. This reflects a lower myocardial oxygen demand offering additional cardioprotection in these high-risk patients.

1. American College of Sports Medicine. Physical activity, physical fitness and hypertension: position stand. *Med Sci Sports Exerc* 1993;25:i–x.
2. Papademetriou V, Kokkinos PF. The role of exercise in the control of hypertension and cardiovascular risk. *Current Opin Nephrology Hyperten* 1996;5:459–462.
3. Kokkinos PF, Narayan P, Papademetriou V. Exercise training and hypertension in adult patients. *Cardiology in the Elderly* 1994;2:433–438.
4. Kokkinos PF, Narayan P, Colleran DO, Pittaras A, Notargiacomo A, Reda D, Papademetriou V. Effects of regular exercise on BP and left ventricular hypertrophy in African-American men with severe hypertension. *New Engl J Med* 1995;333:1462–1467.

Elevated Soluble CD14 Receptors and Altered Cytokines in Chronic Heart Failure

Stefan D. Anker, MD, Karl R. Egerer, MD, PhD, Hans-Dieter Volk, MD, Wolfgang J. Kox, MD, PhD, Philip A. Poole-Wilson, MD, and Andrew J.S. Coats, DM

Recently, it has been recognized that patients with chronic heart failure (CHF) exhibit immune activation and that this could be related to general wasting (i.e., cardiac cachexia) and poor prognosis.[1–3] A direct detrimental influence of tumor necrosis factor (TNF)-α on the failing human heart has been suggested.[4] Neither in patients nor in any animal models has the link between a pathogenic process and cytokine activation in CHF been documented. The cause of TNF-α activation in CHF is also unknown. Intestinal edema from increased mesenteric venous pressure may occur in CHF, even in patients well treated with diuretics. We hypothesized that this mesenteric venous congestion leads to increased bowel permeability, then bacterial translocation, then endotoxin release; the increased endotoxin challenge then causes immune activation with increased TNF-α production (Figure 1). To test this hypothesis, soluble CD14 levels (indicative of endotoxin-cell interaction and shedding from the cell membrane[5]) were measured in patients with CHF and healthy controls. Other cytokines were also analyzed, because they can regulate the expression of CD14 receptors (e.g., interferon [IFN]-γ[6]) or TNF-α production (e.g., interleukin [IL]-10[7,8]) and to characterize the pattern of general immune activation further.

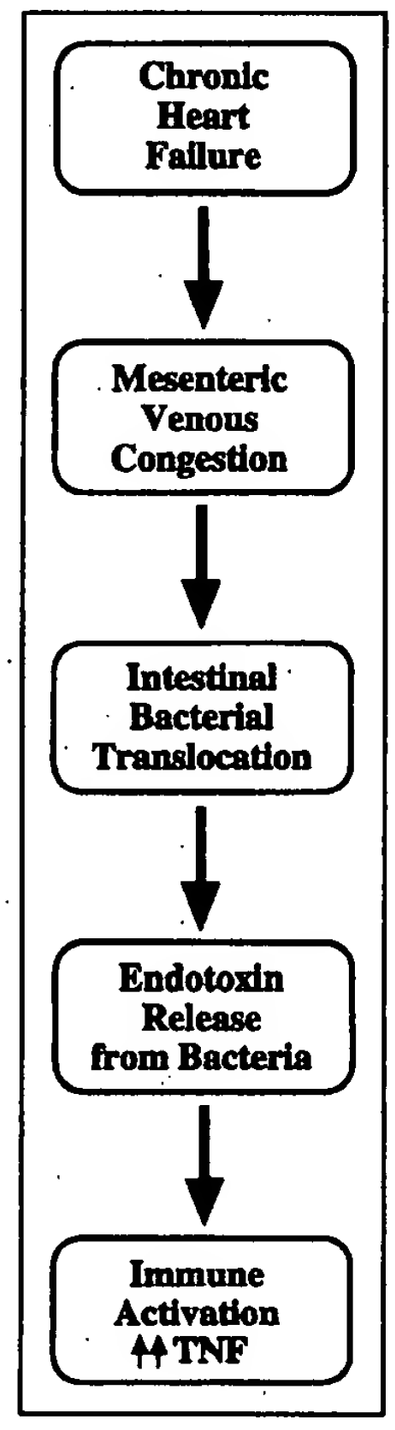


FIGURE 1. A hypothetical sequence of events leading to immune activation in patients with CHF.

From the Department of Cardiac Medicine, National Heart and Lung Institute, London, United Kingdom; Department of Anaesthesiology and Intensive Care Medicine; and Department of Immunology, University Hospital Charité, Humboldt University Berlin, Berlin, Germany. Dr. Anker's address is: Department of Cardiac Medicine, National Heart and Lung Institute London, Dovehouse Street, London SW3 6LY, UK.

Manuscript received September 4, 1996; revised manuscript received and accepted January 17, 1997.

0002-9149/97/$17.00
PII S0002-9149(97)00159-8

TABLE I Comparison of Healthy Controls and Patients With Chronic Heart Failure (CHF): Cytokines, Soluble Receptors, and Adhesion Molecules (mean ± SEM)

	Controls	Chronic Heart Failure	p Value
No. of patients	17	47	—
Soluble CD14 receptor (ng/ml)	2,714 ± 121	3,401 ± 134	0.0048
TNF-α (pg/ml)	7.05 ± 0.67	10.66 ± 1.34	0.12
Soluble TNF receptor 1 (pg/ml)	629 ± 59*	1,323 ± 112†	0.0010
Soluble TNF receptor 2 (pg/ml)	1,972 ± 250*	2,626 ± 163†	0.046
Interleukin-1β (pg/ml)	0.23 ± 0.06*	0.35 ± 0.06†	0.32
Interleukin-6 (pg/ml)	0.97 ± 0.17*	3.62 ± 0.47†	0.0024
Interleukin-10 (pg/ml)	5.31 (+1.46, −1.14)	1.87 (+0.57, −0.44)	0.030
Interferon-γ (IU/ml)	0.79 ± 0.06†	0.66 ± 0.03	0.041
Soluble intercellular adhesion molecule 1 (ng/ml)	277 ± 13	383 ± 13	<0.0001
Soluble endothelialleukocyte adhesion molecule 1 (ng/ml)	37 ± 3	49 ± 3	0.018
White cell count (Gpt/L)	5.1 ± 0.3	7.1 ± 0.3	0.0009
Erythrocyte sedimentation rate (mm/h)	4 ± 1	21 ± 3	0.0004

*Result for 1 missing subject; †Result for 2 missing subjects.

• • •

Seventeen healthy volunteers and 47 CHF patients (of similar ages: 56 ± 2 vs 61 ± 2 years, p = 0.15) were studied. The etiology of CHF was ischemic in 29 patients and 18 patients had idiopathic-dilated cardiomyopathy. The diagnosis of CHF was based on symptomatic exercise intolerance, cardiomegaly, and documented left ventricular dysfunction. No subject had clinical signs of infection, rheumatoid arthritis, or cancer. Patients had a mean left ventricular ejection fraction of 26 ± 2%, 4 patients were in New York Heart Association functional class I, 13 in class II, 24 in class III, and 6 in class IV. Peak oxygen consumption was reduced in patients with CHF compared with controls (17.1 ± 1.0 vs 35.5 ± 1.9 ml/kg/min, p < 0.0001). No patient had severe renal dysfunction (creatinine 131 ± 7 μmol/L, range 68–254). In patients with CHF cachexia was defined on the basis of documented nonintentional nonedematous weight loss of 9% to 36% compared with premorbid normal weight (mean loss 15.5 ± 1.5%, i.e., 7 to 30 kg [mean 12 ± 1 kg] over 1 to 11 years [mean 3 ± 1]) with a body weight of 82 ± 1.7% of ideal. The 25 weight-stable patients with CHF had a mean weight of 104.2 ± 2.8% of ideal. All patients were clinically stable for at least 6 weeks before the study and on optimal drug treatment, mostly consisting of diuretics (n = 45, mean frusemide equivalent dose 126 ± 15 mg) and/or angiotensin-converting enzyme inhibitors (n = 40). All subjects gave written informed consent, and the protocol was approved by the local ethics committee.

Commercially available enzyme-linked immunosorbent assay (ELISA) test kits were used for standard venous blood samples taken between 9 and 10 A.M., after 12 hours fasting and 20 minutes of supine rest. After centrifugation, aliquots were stored at −70°C until analysis. Using test kits from R&D Systems (Minneapolis, Minnesota) soluble TNF receptor 1 (sensitivity 25 pg/ml), soluble TNF receptor 2 (sensitivity 2 pg/ml), IL-1β (sensitivity 0.100 pg/ml), IL-6 (sensitivity 0.094 pg/ml), soluble intercellular adhesion molecule-1 (sensitivity 7 ng/ml), and soluble endothelial-leukocyte adhesion molecule-1 (sensitivity 2 ng/ml) were measured. Total TNF-α (Medgenix, Fleurus, Belgium; lower limit of detectability 3.0 pg/ml, test not influenced by soluble TNF receptors), IL-10 (PerSeptive Diagnostics, Cambridge, Massachusetts, sensitivity 0.7 pg/ml), IFN-γ (IRMA, Medgenix, Fleurus, Belgium, sensitivity 0.20 IU/ml), and CD14 levels (IBL, Hamburg, Germany, sensitivity 1 ng/ml, ELISA test kit[9]) were also analyzed. In some subjects not all cytokines could be measured and therefore data points are missing: for 2 controls and 1 patient (IL-1β, IL-6, soluble TNF receptor 1 and 2), and in 1 control only IFN-γ. Unpaired Student's *t* tests and Mann–Whitney U test were used where appropriate. Because of a skewed distribution, IL-10 results were log-transformed for analyses (therefore, asymmetric mean values). A probability value of p <0.05 was considered significant. Data are presented as mean ± SEM.

Patients with CHF had increased soluble CD14 (p <0.005), soluble TNF receptor 1 (p = 0.001) and 2 (p <0.05), IL-6 (p <0.003), intracellular adhesion molecule-1 (p <0.0001), and endothelial-leukocyte adhesion molecule-1 levels (p <0.02) compared with controls, but reduced IFN-γ and IL-10 levels (both p <0.05, Table I). The 22 cachectic patients with CHF showed markedly increased TNF-α (15.4 ± 2.5 vs 6.5 ± 0.5 pg/ml, p = 0.0005) and soluble CD14 levels (3,837 ± 207 vs 3,018 ± 137 pg/ml, p = 0.0005, Figure 2) compared with the 25 weight-stable patients with CHF.

Fourteen patients with CHF (30%) and only 1 control (6%) had elevated soluble CD14 levels (>2 SDs above mean of controls, i.e., >3,711 pg/ml, mean 4,566 ± 178 pg/ml). Of the 14 patients with CHF with high soluble CD14 levels, 11 (79%) were clinically cachectic, in comparison with only 5 of the 23 patients (22%) with normal CD14 levels (<1 SD above mean control level, i.e., <3,212 pg/ml, mean 2,711 ± 78 pg/ml). The patients with CHF with high soluble CD14 had increased TNF-α (16.6 ± 3.7 vs 7.2 ± 0.9 pg/ml, p = 0.0040), soluble TNF receptor 1 (1,924 ± 201 vs 857 ± 104 pg/ml, p < 0.0001), soluble TNF receptor 2 (3,541 ± 275 vs 2,074 ± 199 pg/ml, p <0.0001), intracellular adhesion mol-

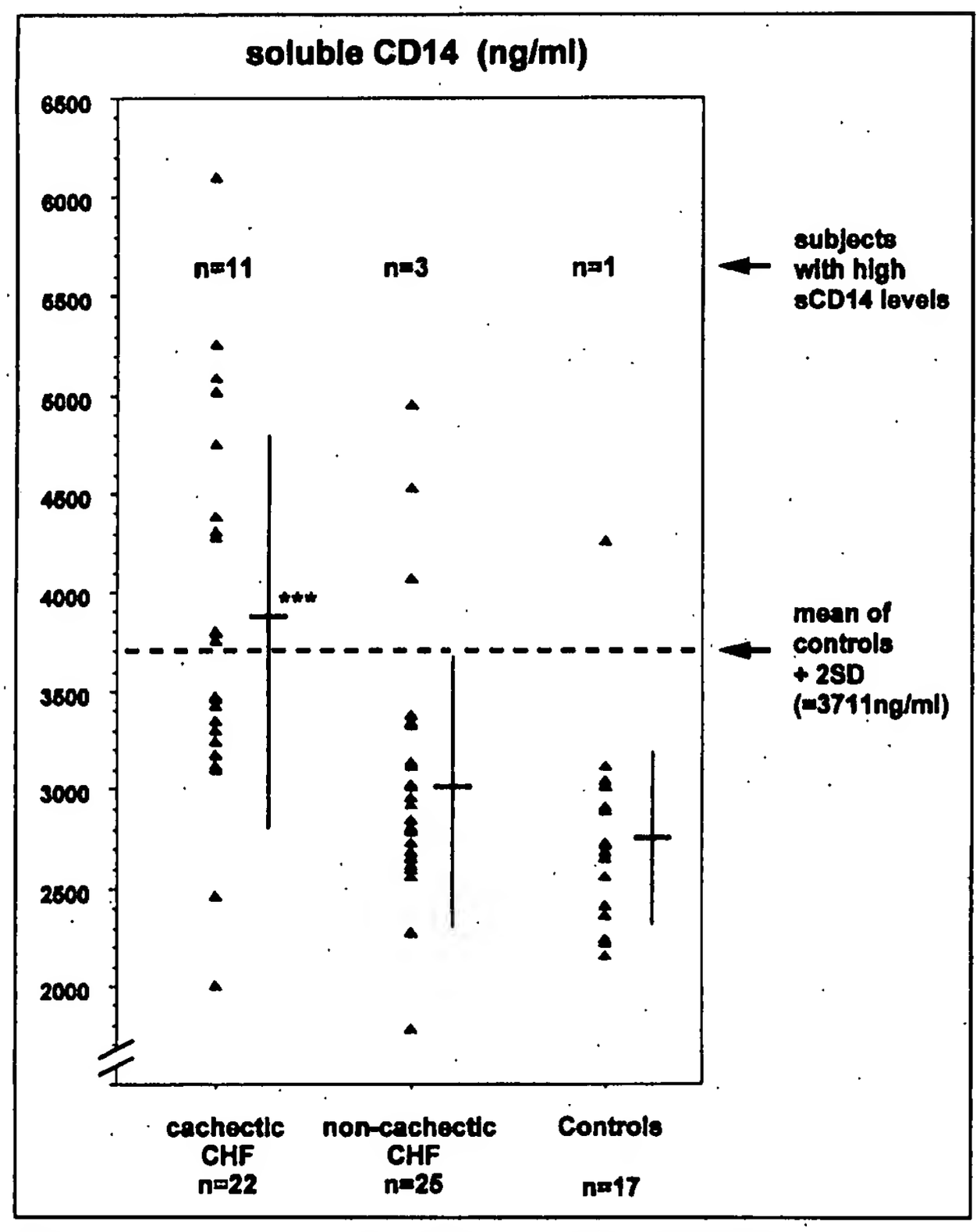


FIGURE 2. Soluble CD14 (sCD14) levels in cachectic and noncachectic patients with CHF compared with healthy controls *bars*, mean ± SD. ***p <0.001 versus noncachectic patients with CHF and controls.

ecule-1 (435 ± 20 vs 354 ± 19 ng/ml, p = 0.0048), and erythrocyte sedimentation rate (35 ± 7 vs 14 ± 2 mm/h, p = 0.0007). A trend for increased IL-6 (4.82 ± 1.00 vs 3.14 ± 0.71 pg/ml, p = 0.074) was found, but endothelial-leukocyte adhesion molecule-1 (51 ± 4 vs 47 ± 4 ng/ml), IL-10 (2.33 (+2.11, −1.11) vs 2.04 (+0.62, −0.48) pg/ml), IFN-γ (0.67 ± 0.04 vs 0.70 ± 0.05 IU/ml), and white cell count (7.6 ± 0.6 vs 6.8 ± 0.5 Gpt/L) were similar in the 2 groups of patients with CHF. The patients with CHF with high soluble CD14 levels compared with the patients with low soluble CD14 were older (66.7 ± 3.1 vs 56.5 ± 2.5 years, p <0.02), but the clinical disease characteristics of these 2 CHF groups were similar: peak oxygen consumption (15.8 ± 1.9 vs 18.9 ± 1.4 ml/kg/min, p = 0.20), exercise time (444 ± 53 vs 479 ± 45 seconds, p = 0.63), radionuclide left ventricular ejection fraction (29 ± 4% vs 27 ± 5%, p = 0.33), and functional New York Heart Association class (2.7 ± 0.2 vs 2.6 ± 0.2, p = 0.60).

There were strong correlations between soluble CD14 levels and soluble TNF receptor 1 (in all subjects: r = 0.71, in all patients with CHF: r = 0.68), soluble TNF receptor 2 (all subjects: 0.62, CHF: r = 0.60, all p <0.0001), and TNF-α (all subjects: r = 0.53, p <0.0001, CHF: r = 0.52, p = 0.0002) (Figure 3). By multivariate analyses, these relationships of soluble CD14 with TNF-α and with soluble TNF receptors were independent of the severity of heart failure (peak oxygen consumption, left ventricular ejection fraction, and functional class), age, and creatinine levels.

• • •

This study shows that soluble CD14 receptor levels are increased in some patients with CHF, especially in those with cachexia. The patients with increased soluble CD14 levels showed marked immune activation, indicated by increased levels of TNF-α, soluble TNF receptor 1, soluble TNF receptor 2, and intracellular adhesion molecule-1 (all p <0.005), but IL-10 and IFN-γ, and conventional parameters of clinical CHF severity were similar in patients with high- and low-soluble CD14 levels. Strong correlations of soluble CD14 levels with soluble TNF receptor 1, soluble TNF receptor 2, and total TNF-α levels were found. Taken together, these findings suggest that endotoxin is involved in the immune activation in patients with CHF.

The presence of increased amounts of soluble CD14 levels can be indicative of the amount of endotoxin interacting with monocytes and/or macrophages.[5] Endotoxin (i.e., lipopolysaccharide [LPS]) is a strong stimulant of TNF production and release by monocytes and/or macrophages.[10] The complex of LPS and LPS-binding protein acts via a 55-kD protein on the surface of mononuclear phagocytes (i.e., CD14). Intestinal edema from increased mesenteric venous pressures may occur in CHF, leading to chronically increased uptake of endotoxin as a consequence of increased bowel permeability and bacterial translocation (Figure 1). In patients with CHF this mechanism has not been investigated before. The patients with CHF had reduced activity of possibly protective cytokine pathways (i.e., IL-10 and IFN-γ). This suggests that an immune-regulatory dysfunction is present in some patients with CHF which might contribute to an increased sensitivity to chronic bacterial translocation. In response to bacterial translocation and repeated endotoxin challenge, TNF production may increase, and subsequently, a more general chronic immune activation may result. Most of the patients with CHF exhibiting immune activation were also clinically cachectic, confirming previous work.[1]

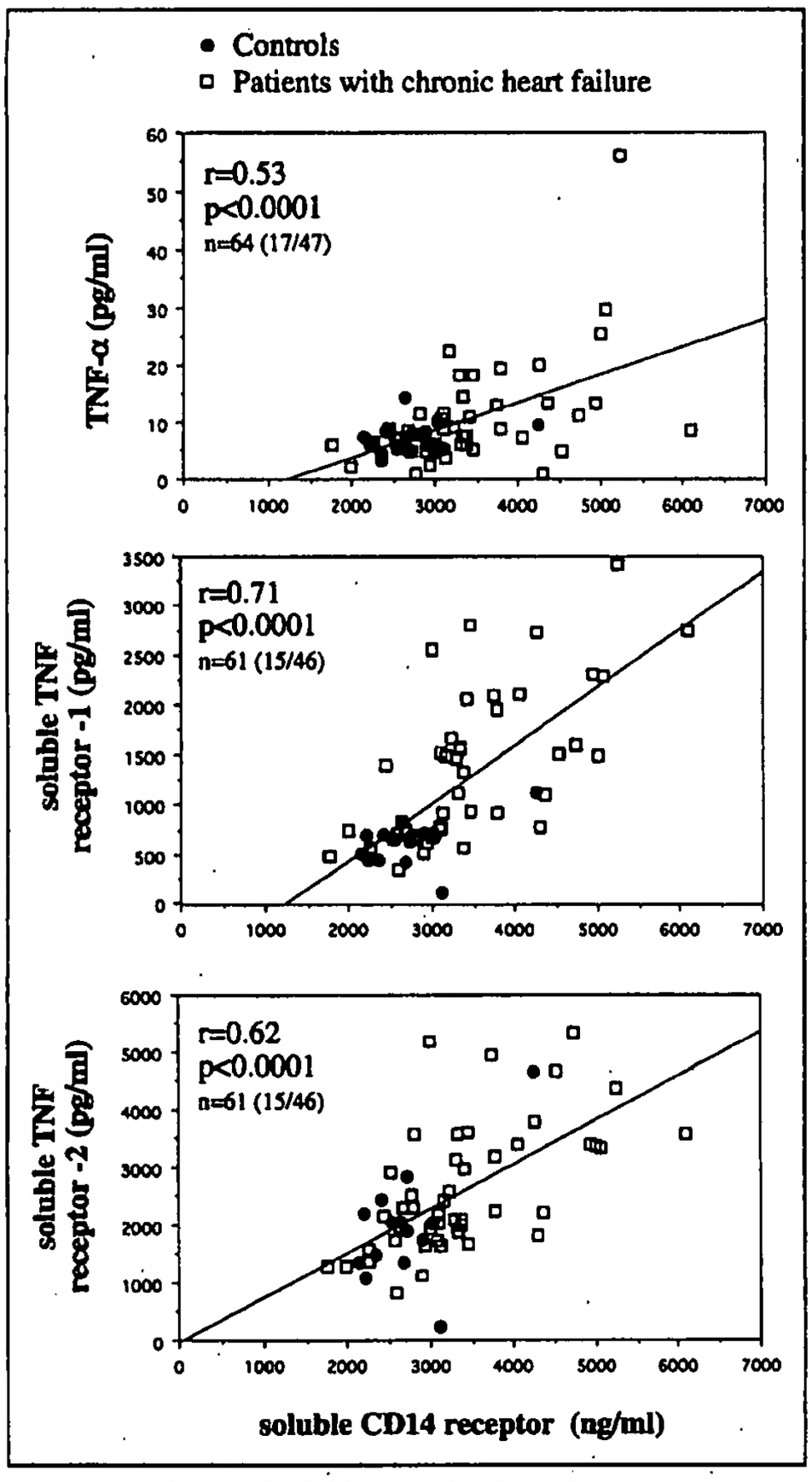


FIGURE 3. Relation of soluble CD14 levels and tumor necrosis factor-α (TNF-α), and to soluble TNF receptors 1 and 2 (sTNFR 1 and 2) in healthy controls and patients with heart failure. TNF-α = 17 controls, 47 patients; sTNFR1 and sTNFR2 = 15 controls, 46 patients.

This study is limited by the fact that TNF-α could be elevated due to other causes, then also causing CD14 shedding. This has not been demonstrated yet. The pharmacologic agents PMA and calcium ionophore A23187, anti-CD14 antibodies, and more importantly bacterial LPS and IFN-γ were in vitro able to down-regulate cell surface CD14 by shedding.[11] In our patients IFN-γ was lower than in controls and did not differ between the groups with high- and low-soluble CD14. Anti-CD14 antibodies and endotoxin itself were not measured. We found that the patients with CHF with high CD14 levels and immune activation had also increased erythrocyte sedimentation rates, arguing for the presence of low-grade chronic inflammation.

The suggested hypothesis of immune activation in CHF secondary to intestinal bacterial translocation may not explain immune activation in all cases. Different mechanisms may work simultaneously. The following mechanisms could theoretically cause increased TNF-α levels. (1) When peripheral blood flow is reduced in CHF, local ischemia and hypoxia may cause monocyte and/or macrophage stimulation. In support of this it was shown that peripheral vasodilator capacity in CHF is inversely related to TNF-α levels,[12] although the known detrimental actions of TNF-α on the endothelium[10] may also partially explain these findings. In a recent study immune activation in 78 stable patients with CHF was compared with controls,[13] and only IL-6 was found to be increased in CHF and it correlated with conventional markers of disease severity (but with no mention of the degree of wasting in these patients). IL-6 activation can be attributed to the peripheral hypoxic conditions[14] that frequently occur in CHF,[15] whereas hypoxia does not influence the cytokine and/or adhesion molecule release that can be observed secondary to LPS action.[16] Increased levels of soluble TNF receptors and particularly soluble CD14 are, in contrast, not characteristic of hypoxic states, but rather are characteristic of LPS action[17]; (2) Prostaglandin E_2 has been found to be increased in patients with severe CHF,[18] and can directly stimulate the release of TNF-α from monocytes and/or macrophages.[19] In very high concentrations it suppresses TNF release (i.e., it exhibits a biphasic regulation).[19] (3) The failing human heart can directly produce TNF-α.[20]

We hypothesized that a chronic endotoxin challenge may cause immune activation in CHF. Patients with high soluble CD14 levels have markedly increased levels of TNF-α, soluble TNF receptors 1 and 2, and intracellular adhesion molecule-1, supporting this hypothesis.

1. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990;323:236–241.
2. Ferrari R, Bachetti T, Confortini R, Opasich C, Febo O, Corti A, Cassani G, Visioli O. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. *Circulation* 1995;92:1479–1486.
3. Tsutamoto T, Hisanaga T, Fukai D, Wada A, Maeda Y, Kinoshita M. Prognostic value of plasma soluble intercellular adhesion molecule-1 and endothelin-1 concentration in patients with chronic congestive heart failure. *Am J Cardiol* 1995;76:803–808.
4. Torre-Amione G, Kapadia S, Lee J, Bies RD, Lebovitz R, Mann DL. Expression and functional significance of tumor necrosis factor receptors in human myocardium. *Circulation* 1995;92:1487–1493.
5. Ziegler-Heitbrock, Ulevitch RJ. CD14: Cell surface receptor and differentiation marker. *Immunology Today* 1993;14:121–125.
6. Lauener RP, Geha RS, Vercelli D. Engagement of the monocyte surface antigen CD14 lymphocyte function-associated antigen-1/intracellular adhesion molecule-1-dependent homotypic adhesion. *J Immunol* 1990;145:1390–1394.
7. Bogdan C, Vodovotz Y, Nathan C. Macrophage deactivation by interleukin-10. *J Exp Med* 1991;174:1549–1555.
8. Howard M, Muchamuel T, Andrade S, Menon S. Interleukin 10 protects mice from lethal endotoxemia. *J Exp Med* 1993;177:1205–1208.
9. Grunwald U, Krüger C, Westermann J, Lukowsky A, Ehlers M, Schütt C. An enzyme-linked immunosorbent assay for the quantification of solubilized CD14 in biological fluids. *J Immunol Meth* 1992;155:225–232.
10. Tracey KJ, Cerami A. Tumor necrosis factor, other cytokines and disease. *Ann Rev Cell Biol* 1994;10:317–343.
11. Bazil V, Stroinger JL. Shedding as a mechanism of down-modulation of CD14 on stimulated human monocytes. *J Immunol* 1991;147:1567–1574.
12. Anker SD, Swan J, Felton C, Volterrani M, Chua TP, Poole-Wilson PA, Coats AJS. TNF-α as predictor of peak leg blood flow in chronic heart failure (abstr). *Circulation* 1995;92(suppl 1):I-430.

13. Munger MA, Johson B, Amber IJ, Callahan KS, Gilbert EM. Circulating concentrations of proinflammatory cytokines in mild or moderate heart failure secondary to ischemic or ideopathic dilated cardiomyopathy. *Am J Cardiol* 1996;77:723–727.
14. Yan SF, Tritto I, Pinsky D, Liao H, Huang J, Fuller G, Brett J, May L, Stern D. Induction of interleukin-6 (IL-6) by hypoxia in vascular cells. *J Biol Chem* 1995;270:11463–11471.
15. Munger MA, Stanek EJ, Nara AR, Strohl KP, Decker MJ, Nair RN. Arterial oxygen saturation in chronic congestive heart failure. *Am J Cardiol* 1994;73:180–185.
16. Klein CL, Kohler H, Bittinger F, Otto M, Hermanns I, Kirkpatrick CJ. Comparative studies on vascular endothelium in vitro. 2. Hypoxia: its influences on endothelial cell proliferation and expression of cell adhesion molecules. *Pathobiology* 1995;63:1–8.
17. Eggesbo JB, Hjermann I, Lund PK, Joo GB, Ovstebo R, Kierulf P. LPS-induced release of IL-1 beta, IL-6, IL-8, TNF-alpha and sCD14 in whole blood and PBMC from persons with high or low levels of HDL-lipoprotein. *Cytokine* 1994;6:521–529.
18. Dzau VJ, Packer M, Lilly LS, Swartz SL, Hollenberg NK, Williams GH. Prostaglandins in severe congestive heart failure: relation to activation of the renin-angiotensin system and hyponatremia. *N Engl J Med* 1984;310:347–352.
19. Renz H, Gong J-H, Schmidt A, Nain M, Gemsa D. Release of tumor necrosis factor-α from macrophages: enhancement and suppression are dose-dependently regulated by prostaglandin E_2 and cyclic nucleotides. *J Immunol* 1988;141:2388–2393.
20. Torre-Amione G, Kapadia S, Lee J, Durand J-B, Bies RD, Young JB, Mann DL. Tumor necrosis factor-α and tumor necrosis factor receptors in the failing human heart. *Circulation* 1996;93:704–711.

Transcatheter Occlusion of Native Persistent Ductus Arteriosus Using Conventional Gianturco Coils

Mazeni Alwi, MRCP, Lim M. Kang, MRCP, Hasri Samion, MD, Haifa A. Latiff, MD, Geetha Kandavel, MRCP, and Robayaah Zambahari, FRCP

Transcatheter closure of small- to moderate-sized persistent ductus arteriosus (PDA) is well established as a procedure of first choice in many institutions. The Rashkind double umbrella device has been the most widely used and evaluated.[1–3] The Gianturco coil has been in clinical use for 2 decades.[4] However, its application for the closure of PDA is comparatively recent. Although it is not specifically designed for this purpose, and hence the variations in technique, its immediate and short-term results have been encouraging.[5–9] We describe our experience in transcatheter closure of native PDA transvenously using Gianturco coils in 211 patients.

• • •

Between December 1994 and July 1996, 211 patients with native PDA who had continuous murmurs were subjected to this procedure. The median age and weight were 4.3 years (range 0.6 to 36.0) and 14.0 kg (range 5.1 to 53.0). One patient with additional pulmonary valve stenosis underwent PDA occlusion at the same time following successful pulmonary valvuloplasty, and another has severe factor XII deficiency. The procedure was performed under general anesthesia in the smaller children. The narrowest internal diameter of the ductus was measured on the lateral projection of the descending aortogram. Depending on the number of coils to be deployed, 1 to 5 4Fr sheaths were inserted in the femoral veins (up to 3 sheaths per vein). No patients were excluded on the basis of ductal morphology. Ductuses >5.0 mm were excluded. The technique described below evolved during the initial learning curve of 25 patients and was adhered to thereafter for the rest of the series.

Gianturco coils (Cook, Bloomington, Indiana) 5 cm long and with helical diameters of 5 mm or 8 mm were used. The following guideline was used in determining the number of coils in relation to ductal size: 1 coil for ductuses <1.5 mm, 2 coils for 1.6 to 2.5 mm, 3 coils for 2.6 to 3.5 mm, 4 coils for 3.6 to 4.0 mm, and ≥5 coils for ductuses >4.0 mm, taking into consideration an exponential increase in cross-sectional area for a given increase in diameter. Accordingly, 1 to 5 4Fr multipurpose catheters were placed simultaneously across the ductus, 1 catheter for each coil. The coils were deployed as in a previously described technique.[7] In cases requiring multiple coils, the terminal 0.5 to 1.0 cm of each coil was kept within the catheters in the pulmonary artery and final deployment was carried out sequentially once the coil's position was deemed stable. This was to facilitate retrieval if the loops of coil deployed on the aortic end slipped through the ductus. As far as possible, only 1/2 to 3/4 of a loop was deployed on the pulmonary end of the ductus and the major portion of the coil was seated within the ampulla to minimize left pulmonary artery stenosis. A repeat descending aortogram was performed 10 minutes after the procedure. In the rare cases of significant residual shunt, the ductus was recrossed anterogradely, or if this was not possible, retrogradely, and additional coils were deployed. Clinical and Doppler echocardiography evaluation to detect residual shunt and to measure left pulmonary artery and descending aortic velocities were performed at 24 hours after the procedure and serially at 3, 6, 12, and 18 months follow-up. An option for reocclusion was put forward if residual shunt remained at 6 months. During the study period, 211 patients were subjected to this procedure. For the entire series, procedural failure occurred in 7 patients (3%), 6 of them in the initial learning curve of the first 25 patients. In these 6 patients simultaneous multiple catheter technique was not used and only the smaller 5-mm diameter coils were deployed, resulting in slippage into the pul-

From the National Heart Institute, Kuala Lumpur, Malaysia. Dr. Alwi's address is: Department of Cardiology, National Heart Institute, 145, Jalan Tun Razak, 50400 Kuala Lumpur, Malaysia. Manuscript received October 8, 1996; revised manuscript received and accepted January 29, 1997.

0002-9149/97/$17.00
PII S0002-9149(97)00160-4

Connecting via Winsock to STN

Welcome to STN International! Enter x:X

LOGINID:SSSPTA1644PNH

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS 3	JAN 16	CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS 4	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS 5	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS 6	JAN 22	CA/CAplus updated with revised CAS roles
NEWS 7	JAN 22	CA/CAplus enhanced with patent applications from India
NEWS 8	JAN 29	PHAR reloaded with new search and display fields
NEWS 9	JAN 29	CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS 10	FEB 15	PATDPASPC enhanced with Drug Approval numbers
NEWS 11	FEB 15	RUSSIAPAT enhanced with pre-1994 records
NEWS 12	FEB 23	KOREAPAT enhanced with IPC 8 features and functionality
NEWS 13	FEB 26	MEDLINE reloaded with enhancements
NEWS 14	FEB 26	EMBASE enhanced with Clinical Trial Number field
NEWS 15	FEB 26	TOXCENTER enhanced with reloaded MEDLINE
NEWS 16	FEB 26	IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS 17	FEB 26	CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases
NEWS 18	MAR 15	WPIDS/WPIX enhanced with new FRAGHITSTR display format
NEWS 19	MAR 16	CASREACT coverage extended
NEWS 20	MAR 20	MARPAT now updated daily
NEWS 21	MAR 22	LWPI reloaded
NEWS 22	MAR 30	RDISCLOSURE reloaded with enhancements
NEWS 23	APR 02	JICST-EPLUS removed from database clusters and STN
NEWS 24	APR 30	GENBANK reloaded and enhanced with Genome Project ID field
NEWS 25	APR 30	CHEMCATS enhanced with 1.2 million new records
NEWS 26	APR 30	CA/CAplus enhanced with 1870-1889 U.S. patent records
NEWS 27	APR 30	INPADOC replaced by INPADOCDB on STN
NEWS 28	MAY 01	New CAS web site launched

NEWS EXPRESS	NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * * *

```
FILE 'HOME' ENTERED AT 09:26:38 ON 03 MAY 2007

=> file medline embase biosis scisearch caplus
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'MEDLINE' ENTERED AT 09:27:00 ON 03 MAY 2007

FILE 'EMBASE' ENTERED AT 09:27:00 ON 03 MAY 2007
Copyright (c) 2007 Elsevier B.V. All rights reserved.

FILE 'BIOSIS' ENTERED AT 09:27:00 ON 03 MAY 2007
Copyright (c) 2007 The Thomson Corporation

FILE 'SCISEARCH' ENTERED AT 09:27:00 ON 03 MAY 2007
Copyright (c) 2007 The Thomson Corporation

FILE 'CAPLUS' ENTERED AT 09:27:00 ON 03 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

=> s ursodeoxycholic acid
L1         18689 URSODEOXYCHOLIC ACID

=> s l1 and diuretic
L2            66 L1 AND DIURETIC

=> dup remove l22
L22 IS NOT VALID HERE
The L-number entered has not been defined in this session, or it
has been deleted.  To see the L-numbers currently defined in this
session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> dup remove l2
PROCESSING COMPLETED FOR L2
L3             59 DUP REMOVE L2 (7 DUPLICATES REMOVED)

=> d l3 1-59 cbib abs

L3   ANSWER 1 OF 59  EMBASE  COPYRIGHT (c) 2007 Elsevier B.V. All rights
     reserved on STN
2007144810  EMBASE  Hypertension and fatty liver: Guilty by association?.
     Brookes M.J.; Cooper B.T.. B.T. Cooper, Gastroenterology Unit, City
     Hospital, Birmingham, United Kingdom. Journal of Human Hypertension  Vol.
     21, No. 4, pp. 264-270  2007.
     Refs: 96.
     ISSN: 0950-9240. E-ISSN: 1476-5527. CODEN: JHHYEN
     1002148. Pub. Country: United Kingdom. Language: English. Summary
     Language: English.
     Entered STN: 20070425. Last Updated on STN: 20070425
AB   Essential hypertension is associated with the metabolic syndrome, insulin
     resistance and the development of fatty liver.  Fatty liver disease is a
     spectrum of liver diseases ranging from simple hepatic steatosis through
     steato-hepatitis to cirrhosis and hepatoma.  The purpose of this review is
     to discuss the evidence for an association between essential hypertension
     and non-alcoholic fatty liver disease, and to consider the diagnosis and
     management of non-alcoholic fatty liver disease.  We conclude that it is
     important to consider the diagnosis of fatty liver disease in hypertensive
     patients, to measure the liver function tests at diagnosis and not to
     ignore minor elevations of serum aminotransferases.  Hypertensive patients
     with raised liver enzymes should be referred for further assessment,
     particularly if risk factors for progressive liver disease, such as
```

obesity and diabetes, are present.

L3 ANSWER 2 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006608677 EMBASE Characterization of the uptake mechanism for a novel loop diuretic, M17055, in Caco-2 cells: Involvement of organic anion transporting polypeptide (OATP)-B. Nishimura T.; Kubo Y.; Kato Y.; Sai Y.; Ogihara T.; Tsuji A.. A. Tsuji, Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan. tsuji@kenroku.kanazawa-u.ac.jp. Pharmaceutical Research Vol. 24, No. 1, pp. 90-98 2007.
Refs: 35.
ISSN: 0724-8741. E-ISSN: 1573-904X. CODEN: PHREEB
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20070123. Last Updated on STN: 20070123

AB Purpose. M17055 is under development as a novel loop diuretic for oral administration. To investigate the molecular mechanism of its gastrointestinal absorption, we initially aimed to clarify the mechanism of uptake of M17055 by Caco-2 cells, focusing on possible involvement of OATP-B (SLCO2B1), which is localized in the apical membranes of human intestinal epithelial cells. Materials and Methods. The uptake of [(14)C]M17055 by Caco-2 cells cultured on multi-well dishes was measured after cultivation for 14 days. Uptake of [(14)C]M17055 by HEK293 cells stably expressing OATP-B (HEK293/OATP-B cells) was also examined. Results. M17055 uptake by Caco-2 cells was saturable, and was inhibited by various organic anions, including other loop diuretics, and several bile acids. Uptake of M17055 by HEK293/OATP-B cells was much higher than that by mock cells. The inhibitory profiles of various organic anions and the estimated K (m) values for M17055 uptake were similar in Caco-2 and HEK293/OATP-B cells. Moreover, the values of inhibition constants of several inhibitors for M17055 uptake were comparable in the two cell lines. Conclusion. Our data suggest that OATP-B plays a major role in the uptake of the novel loop diuretic M17055 from apical membranes in Caco-2 cells. .COPYRGT. 2006 Springer Science+Business Media, Inc.

L3 ANSWER 3 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006524409 EMBASE Symptomatic hepatic hemangioendothelioma in a newborn. Jothilakshmi K.; Matthai J.; Paul S.; Singal A.K.. Dr. Prof. K. Jothilakshmi, Department of Pediatrics, PSG Institute of Medical Sciences, Peelamedu, Coimbatore 641 004, psg_peds@yahoo.com. Indian Pediatrics Vol. 43, No. 10, pp. 908-910 2006.
Refs: 9.
ISSN: 0019-6061. E-ISSN: 0019-6061. CODEN: INPDAR
Pub. Country: India. Language: English. Summary Language: English.
Entered STN: 20061110. Last Updated on STN: 20061110

AB A case of hepatic hemangioendothelioma presenting as congestive cardiac failure in a neonate is reported. There was also evidence of platelet consumption. The case was managed successfully with oral prednisolone, resulting in improvement of symptoms and tumor regression over 3 months.

L3 ANSWER 4 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2006577787 EMBASE Liver involvement in cystic fibrosis. Brigman C.; Feranchak A.. Dr. A. Feranchak, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Children's Medical Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, United States. drew.feranchak@utsouthwestern.edu. Current Treatment Options in Gastroenterology Vol. 9, No. 6, pp. 484-496 2006.
Refs: 62.
ISSN: 1092-8472. CODEN: CTOGA7
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20061213. Last Updated on STN: 20061213

AB The hepatobiliary manifestations of cystic fibrosis (CF) encompass a broad clinical spectrum, from mild steatosis, associated with poor nutrition, to multilobular cirrhosis and the complications of portal hypertension. The factor(s) responsible for the development and progression of liver disease in a subset of patients with CF are unknown. Liver disease can be silent and progressive, manifesting only with complications associated with cirrhosis and portal hypertension. Clinical evaluation for detecting and monitoring the progression of liver disease includes the following: physical examination of the liver, biochemical tests of Liver function and injury, and radiological imaging with abdominal ultrasonography. Careful monitoring should take place in all patients with CF, as currently, there are no sensitive and/or specific historical or biochemical markers to predict who is at risk for the development of Liver disease. Current treatment options for CF-associated liver disease are very Limited. The bile acid ursodeoxycholic acid may improve biochemical parameters of liver disease, but its tong-term efficacy in preventing the progression of liver disease in CF is unproven. Treatment therefore rests on optimizing nutritional status; correcting fat-soluble vitamin, essential fatty acid, and other mineral deficiencies; and treating complications of end-stage liver disease, such as pruritis, ascites, and portal hypertension. Copyright .COPYRGT. 2006 by Current Science Inc.

L3 ANSWER 5 OF 59 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2006:447750 Document No.: PREV200600454976. Intrahepatic biliary cysts presenting before hepatic portoenterostomy in biliary atresia. Mas, Emmanuel; Alvarez, Fernando; Oligny, Luc L.; Martin, Steven [Reprint Author]. Univ Montreal, Hop St Justine, Div Gastroenterol Hepatol and Nutr, Dept Pediat, 3175 Cote St Catherine, Montreal, PQ H3T 1C5, Canada. steven.martin@umontreal.ca. JPGN Journal of Pediatric Gastroenterology and Nutrition, (APR 2006) Vol. 42, No. 4, pp. 440-442.
CODEN: JPGND6. ISSN: 0277-2116. Language: English.

L3 ANSWER 6 OF 59 CAPLUS COPYRIGHT 2007 ACS on STN
2005:14190 Document No. 142:100401 Composite product obtainable by co-grinding of an active principle with a N-vinyl-2-pyrrolidone/vinyl acetate copolymer. Olivieri, Aldo; Bonanomi, Michele; Pazzi, Piergiorgio (Bioprogress S.p.A., Italy). PCT Int. Appl. WO 2005000273 A1 20050106, 27 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-IT401 20030627.

AB The present invention describes a method for obtaining composite products comprising an active substance supported by a carrier, in which the carrier is the linear copolymer of N-vinyl-2-pyrrolidone (NVP) with vinyl acetate (VA). The composite products are obtained by co-grinding of the dry mixture of the active substance and of the aforesaid carrier. The composite products thus obtained have better physicochem. properties (lower melting enthalpy and/or lower melting temperature of the active substance) and a higher dissoln. speed with respect to composite products obtained with the same-co-grinding time with other carriers used in prior techniques. Furthermore, the composite products obtained with the technique according to the present invention have the appearance of powders that are easier to work from a pharmaceutical point of view (flow, compression) with respect to composite products previously obtained with other carriers. For example, 16.6 g of nimesulide were mixed with 49.8 g of NVP/VA for 15 min. The powder was then poured into the grinding chamber of a low energy vibrational mill and the grinding was carried out for 2 h.

L3 ANSWER 7 OF 59 CAPLUS COPYRIGHT 2007 ACS on STN

2005:36545 Document No. 142:107463 Treatment of liver disease with active vitamin D compounds. Curd, John G. (Novacea, Inc., USA). U.S. Pat. Appl. Publ. US 2005009793 A1 20050113, 14 pp., Cont.-in-part of Appl. No. PCT/US03/37291. (English). CODEN: USXXCO. APPLICATION: US 2004-841606 20040510. PRIORITY: US 2002-427953P 20021121; WO 2003-US37291 20031121.

AB The invention discloses a method for treating liver disease in an animal by administering an active vitamin D compound, preferably one that accumulates in the liver.

L3 ANSWER 8 OF 59 EMBASE

2005400640 EMBASE The liver in pregnancy: Disease vs benign changes. Wakim-Fleming J.; Zein N.N.. Dr. J. Wakim-Fleming, Department of Gastroenterology and Hepatology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States. Cleveland Clinic Journal of Medicine Vol. 72, No. 8, pp. 713-721 2005.
Refs: 79.
ISSN: 0891-1150. CODEN: CCJMEL
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20050922. Last Updated on STN: 20050922

AB Liver dysfunction in a pregnant woman may be caused by the pregnancy, it may be unrelated to the pregnancy, or it may be a chronic condition that existed before the pregnancy. In any case, the clinical clues of liver dysfunction in pregnancy are not specific, and certain "abnormalities" in liver function tests may represent benign changes of pregnancy. On the other hand, prompt recognition of the signs of liver disease in pregnant patients leads to timely management and may save the life of both mother and baby.

L3 ANSWER 9 OF 59 EMBASE

2005448612 EMBASE Successful liver transplantation in a child with severe portopulmonary hypertension treated with epoprostenol. Laving A.; Khanna A.; Rubin L.; Ing F.; Dohil R.; Lavine J.E.. Dr. J.E. Lavine, Division of Pediatric Gastroenterology and Nutrition, University of California, San Diego, MC 8450, 200 West Arbor Drive, San Diego, CA 92103, United States. jolavine@ucsd.edu. Journal of Pediatric Gastroenterology and Nutrition Vol. 41, No. 4, pp. 466-468 2005.
Refs: 12.
ISSN: 0277-2116. CODEN: JPGND6
Pub. Country: United States. Language: English.
Entered STN: 20051110. Last Updated on STN: 20051110
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L3 ANSWER 10 OF 59 EMBASE

2005178483 EMBASE Fatal course of parvovirus B19-associated myocarditis in a female liver transplant recipient. Jonetzko P.; Graziadei I.; Nachbaur K.; Vogel W.; Pankuweit S.; Zwick R.; Pachinger O.; Poelzl G.. Dr. P. Jonetzko, Clinical Division of Cardiology, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria. patrycja.jonetzko@uklibk.ac.at. Liver Transplantation Vol. 11, No. 4, pp. 463-466 2005.
Refs: 17.
ISSN: 1527-6465. CODEN: LITRFO
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20050505. Last Updated on STN: 20050505

AB Acute myocarditis may result in severe hemodynamic compromise with fatal outcome. Furthermore, recent studies suggest myocarditis as a major cause of sudden unexpected death. A variety of cardiotropic viral, rickettsial, and bacterial infectious agents have been identified to date. Parvovirus B19 (PVB19) is usually benign in childhood, but it may also cause death due to myocarditis. We present here the case of an adult female who presented with fatigue, dyspnea on exertion, and orthostatic dizziness 8 months after successful liver transplantation. Cardiologic work-up,

including left ventricular endomyocardial biopsy, revealed acute myocarditis secondary to PVB19. Since no specific therapy for this virus is available, the patient was treated symptomatically with an angiotensin-converting enzyme inhibitor plus beta-blocker and diuretics. After a period of stabilization, new-onset rapid atrial fibrillation caused acute low-output syndrome within 14 days after hospital admission. The patient eventually died because of refractory cardiogenic shock. In conclusion, to our knowledge this is the first report of PVB19-induced myocarditis confirmed by detection of viral genome in myocardium in a liver transplant recipient. Copyright .COPYRGT. 2005 by the American Association for the Study of Liver Diseases.

L3 ANSWER 11 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2005114816 EMBASE Long-term management of alcoholic liver disease.
Wakim-Fleming J.; Mullen K.D.. Dr. J. Wakim-Fleming, Case W. Reserve School of Medicine, 2580 Metrohealth Drive, Cleveland, OH 44109, United States. jwfleming@metrohealth.org. Clinics in Liver Disease Vol. 9, No. 1, pp. 135-149 2005.
Refs: 93.
ISSN: 1089-3261. CODEN: CLDIF
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20050331. Last Updated on STN: 20050331

AB Despite the epidemics of viral hepatitis C and nonalcoholic fatty liver disease, alcohol remains one of the major causes of liver disease. Commonly, hepatitis C and other liver diseases are found in association with alcohol consumption. This association in many instances is noted to accelerate the progression of liver disease. In many respects, the long-term management of alcoholic liver disease is not dissimilar from the long-term management of patients with cirrhosis from other etiologies. One major element is the abstinence of alcohol use. The ability to maintain sobriety has a major impact on the outcome of patients with alcoholic cirrhosis because maintaining abstinence can lead to significant regression of fibrosis and possibly early cirrhosis. Similarities in managing patients with cirrhosis due to alcohol or cirrhosis from other causes include vaccination to prevent superimposed viral hepatitis and screening for esophageal varices and hepatocellular carcinoma with subsequent appropriate therapy. .COPYRGT. 2005 Elsevier Inc. All rights reserved.

L3 ANSWER 12 OF 59 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2006:68597 Document No.: PREV200600069929. Liver transplantation, rejection and disease recurrence. Beckebaum, S. [Reprint Author]; Cicinnati, V. R.; Broelsch, C. E.. Leuschner, U [Editor]; Broome, U [Editor]; Stiehl, A [Editor]. (2004) pp. 197-200. Falk Symposium:IN HONOUR OF HANS POPPER'S 100TH BIRTHDAY. Publisher: SPRINGER, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS. Series: FALK SYMPOSIUM.
Meeting Info.: 12th International Falk Liver Week. Freiburg, GERMANY. October 15 -21, 2003. Falk Fdn.
ISBN: 0-7923-8793-7(H). Language: English.

L3 ANSWER 13 OF 59 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2004:387427 Document No.: PREV200400387271. Primary biliary cirrhosis and systemic amyloidosis, a new association. Rodriguez-luna, Hector [Reprint Author]; Vargas, Hugo E.; Williams, James; De Petris, Giovanni; Rakela, Jorge; Douglas, David D.. Dept Transplant Med, Mayo Clin Hosp, Phoenix, AZ, 85254, USA. RodriguezLuna.Hector@Mayo.Edu. Digestive Diseases and Sciences, (August 2004) Vol. 49, No. 7-8, pp. 1196-1200. print.
ISSN: 0163-2116 (ISSN print). Language: English.

L3 ANSWER 14 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2004380314 EMBASE Survival of anti-mitochondrial antibody-positive and

-negative primary biliary cirrhosis patients on ursodeoxycholic acid treatment. Koulentaki M.; Moscandrea J.; Dimoulios P.; Chatzicostas C.; Kouroumalis E.A.. kofterid@med.uoc.gr. Digestive Diseases and Sciences Vol. 49, No. 7-8, pp. 1190-1195 2004.
Refs: 37.
ISSN: 0163-2116. CODEN: DDSCDJ
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20040924. Last Updated on STN: 20040924

AB The survival of 85 anti-mitochondrial antibody (AMA)-positive (mean Mayo risk score, 5.11) and 19 AMA-negative (mean Mayo risk score, 4.77) primary biliary cirrhosis patients, under ursodeoxycholic acid not subjected to liver transplantation, was compared with the estimated survival of a simulated control group of untreated patients created with the updated Mayo model and a control group from the general population. In the first 7 years 3 AMA-negative patients died, versus 12 under the Mayo model (P=0.01), and 10 AMA-positive patients, versus 26 under the Mayo model (P<0.005), with 7 expected deaths from the general population (P<0.0001). At 10 years the cumulative survival differed in the treated patients overall (P<0.0001) but not in the early primary biliary cirrhosis (stages I-II) patients compared to the general population. Therefore the survival of our patients treated with ursodeoxycholic acid is higher than that predicted from the Mayo model. Early treatment may prolong survival.

L3 ANSWER 15 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2004518280 EMBASE Treatment of the pruritus of cholestasis. Bergasa N.V.. Dr. N.V. Bergasa, Division of Hepatology, State University of New York, Downstate Medical Center, Box 50, Brooklyn, NY 11203, United States. Nora.Bergasa@downstate.edu. Current Treatment Options in Gastroenterology Vol. 7, No. 6, pp. 501-508 2004.
Refs: 27.
ISSN: 1092-8472. CODEN: CTOGA7
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20041228. Last Updated on STN: 20041228

AB The etiology of the pruritus of cholestasis is unknown. It is inferred that the pruritogen(s) is produced in the liver, excreted in bile, and as a result of cholestasis it accumulates in plasma. It may follow, logically, that the removal of the substance(s) that mediate pruritus leads to its resolution. The problem with this approach, however, is that the substance(s) is unknown; thus, it is not possible to reduce its serum levels specifically. Oral cholestyramine, a resin that is not absorbed, is associated with increased fecal excretion of certain substances, including cholesterol and bile acids. Many patients respond to treatment with cholestyramine with a relief of pruritus, which unfortunately may be temporary, but is well toterated in general and it seems reasonable to prescribe it as an initial therapy. When pruritus is not relieved by resins, the use of opiate antagonists (eg, naloxone and naltrexone) is supported by data from controlled clinical trials. Butorphanol is an agonist at the kappa opioid receptor and an antagonist at the mu opioid receptor with minimal or absent abuse potential. The use of butorphanol spray in selective patients may be a therapeutic alternative. In uncontrolled observations dronabinol, an agonist at the cannabinoid B1 receptor, and sertraline, a serotonin reuptake inhibitor, have been reported to be associated with the relief of pruritus. The cannabinoidergic and serotoninergic systems participate in the mediation of nociception; therefore, there appears to be a rationale for the use of these drugs to treat pruritus. Data from controlled clinical trials on the use of dronabinol and sertraline, however, are not available at present. Copyright .COPYRGT. 2004 by Current Science Inc.

L3 ANSWER 16 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2004265273 EMBASE [Maternal liver diseases during pregnancy].

LEBERERKRANKUNGEN IN DER SCHWANGERSCHAFT: MOLEKULARE PATHOGENESE UND INTERDISZIPLINARES MANAGEMENT. Lammert F.; Rath W.; Matern S.. Dr. F. Lammert, Molekulare und Klinische Hepatologie, Medizinische Klinik III, Universitatsklinikum der RWTH Aachen, Pauwelstrasse 30, 52074 Aachen, Germany. flammert@ukaachen.de. Gynakologe Vol. 37, No. 5, pp. 418-426 2004.
Refs: 34.
ISSN: 0017-5994. CODEN: GYNKAP
Pub. Country: Germany. Language: German. Summary Language: English; German.
Entered STN: 20040709. Last Updated on STN: 20040709

AB A complete spectrum of maternal liver diseases occurs during pregnancy. Many, such as viral hepatitis, are not related to pregnancy. In contrast, women may develop potentially life-threatening liver diseases uniquely related to pregnancy. Beside the syndrome of Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP syndrome), these include the common intrahepatic cholestasis of pregnancy and the very rare acute fatty liver of pregnancy. During the past decade the molecular pathogenesis of these two diseases has been better defined, and mutations in genes encoding the hepatocanalicular phospholipid transporter and enzymes of fatty acid β-oxidation have been identified as genetic risk factors. Furthermore, to optimized obstetric, intensive care and hepatological management, maternal and fetal mortality have decreased significantly.

L3 ANSWER 17 OF 59 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2006:113485 Document No.: PREV200600124712. Parenteral nutrition associated cholelithiasis in very low birth weight infants: Long term clinical and ultrasonographic follow up study. Punnahitananda, Santi [Reprint Author]; Piyawansirikul, Piya; Ketkaew, Krit; Thaithumyanon, Pimolrat; Praisuwanna, Pramote. Chulalongkorn Univ, Fac Med, Dept Pediat, Bangkok 10330, Thailand. Pediatric Research, (APR 2004) Vol. 55, No. 4, Suppl. S, Part 2, pp. 389A.
Meeting Info.: Annual Meeting of the Pediatric-Academic-Societies. San Francisco, CA, USA. May 01 -04, 2004. Pediat Acad Soc.
CODEN: PEREBL. ISSN: 0031-3998. Language: English.

L3 ANSWER 18 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2004229906 EMBASE Multiple hepatic peribiliary cysts with cirrhosis. Seguchi T.; Akiyama Y.; Itoh H.; Tanaka H.; Naganuma S.; Nagaike K.; Uchiyama S.; Kataoka H.. H. Kataoka, Second Department of Pathology, Miyazaki Medical College, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan. Journal of Gastroenterology Vol. 39, No. 4, pp. 384-390 2004.
Refs: 16.
ISSN: 0944-1174. CODEN: JOGAET
Pub. Country: Japan. Language: English. Summary Language: English.
Entered STN: 20040610. Last Updated on STN: 20040610

AB Multiple hepatic peribiliary cysts were found in three autopsy ases of patients who had had underlying liver diseases and obstructive jaundice. Macroscopically, the cysts were visible and present exclusively in the hepatic hilum and larger portal tracts. Histologically, the cysts were of varying size and were lined by a single layer of cuboidal or flattened epithelial cells without atypia. Intimate association between the cysts and peribiliary glands was found in the walls of large bile ducts. All three cases were associated with liver cirrhosis in patients with portal hypertension, and two of the patients had also had hepatocellular carcinoma. These findings support the previous assumption that multiple hepatic peribiliary cysts may be closely related to a portal hypertensive condition. Although peribiliary cysts have been considered to be clinically asymptomatic in general, in one of our patients, the cystic dilatation appeared to have been responsible for the progression of obstructive jaundice. .COPYRGT. Springer-Verlag 2004.

L3 ANSWER 19 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights

reserved on STN
2004079588 EMBASE Endotoxinemia and benzodiazepine-like substances in compensated cirrhotic patients: A randomized study comparing the effect of rifaximine alone and in association with a symbiotic preparation.
Lighthouse J.; Naito Y.; Helmy A.; Hotten P.; Fuji H.; Min C.H.; Yoshioka M.; Marotta F.. F. Marotta, via Pisanello 4, Milan 20146, Japan. fmarchimede@libero.it. Hepatology Research Vol. 28, No. 3, pp. 155-160 2004.
Refs: 31.
ISSN: 1386-6346. CODEN: HPRSFM
S 1386-6346(03)00438-8. Pub. Country: Ireland. Language: English. Summary Language: English.
Entered STN: 20040304. Last Updated on STN: 20040304
AB Aim: The aim of the present investigation was to test study benzodiazepines (BZDs) profile in patients with viral cirrhosis under different combinations of rifaximine and of a novel symbiotic. Methods: Our study groups consisted of 30 patients with a confirmed diagnosis of HCV-related Child B liver cirrhosis. Patients were randomly allocated into three groups: rifaximine 400 mg t.i.d. for 2 weeks; (B) SCM-III (Lactobacillus acidophilus, Lactobacillus helveticus and Bifidobacteria in a ion- and vitamin-enriched medium, Named srl, Italy) 10 ml t.i.d. for 2 weeks; (C) rifaximine 400 mg t.i.d. for 1 week followed by SCM-III 10 ml t.i.d. for 5 weeks. At weekly interval, blood samples were withdrawn to test BZD-like substances, ammonia and endotoxin. Results: Rifaximine treatment brought about a significant early drop of BZDs ($P<0.01$ versus pre-treatment and versus control) till fourth week of observation when a gradual increase took place with return to pre-treatment values at the sixth week. Symbiotic treatment was comparably effective while given to patients but significantly elevated BZDs level were noted starting from the third week. Similar phenomena were noted for endotoxin and ammonia although symbiotic seemed more effective against endotoxin and rifaximine against ammonia increase. However, the sequential treatment rifaximine-symbiotic brought about a sustained normalization of BZDs, ammonia and endotoxin throughout the 6-week study. Conclusion: The present pilot study suggests that a rifaximine-symbiotic regimen could be an effective tool in compensated liver cirrhosis to limit some triggering factors of hepatic encephalopathy while being amenable to long-term use and devoid of significant side effects. .COPYRGT. 2003 Elsevier B.V. All rights reserved.

L3 ANSWER 20 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2004105900 EMBASE [Diagnostic and therapeutic approach to cholestatic liver disease]. ABORDAJE DIAGNOSTICO Y TERAPEUTICO DEL SINDROME COLESTASICO.
Perez Fernandez T.; Lopez Serrano P.; Tomas E.; Gutierrez Ma.L.; Lledo J.L.; Cacho G.; Santander C.; Fernandez Rodriguez C.M.. C.M. Fernandez Rodriguez, Unidad de Aparato Digestivo, Fundacion Hospital Alcorcon, Avda. Budapest 1, 28922 Alcorcon, Madrid, Spain. cfernandez@fhalcorcon.es. Revista Espanola de Enfermedades Digestivas Vol. 96, No. 1, pp. 60-73 2004.
Refs: 55.
ISSN: 1130-0108. CODEN: REDIEM
Pub. Country: Spain. Language: English; Spanish. Summary Language: English; Spanish.
Entered STN: 20040318. Last Updated on STN: 20040318
AB When cholestatic liver disease is present, liver ultrasound should be performed to ascertain if cholestasis is extrahepatic or intrahepatiic. If bile ducts appear dilated and the probability of interventional treatment is high, endoscopic retrograde cholagiopancreatography (ERCP) or trans-hepatic cholangiography (THC) should be the next step. If the probability of interventional therapeutics is low, cholangio-MRI should be performed. Once bile duct dilation and space occupying lesions are excluded, a work up for intrahepatic cholestasis should be started. Some especific clinical situations may be helpful in the diagnostic strategy. If cholestasis occurs in the elderly, drug-induced cholestatic disease

should be suspected, whereas if it occurs in young people with risk factors, cholestatic viral hepatitis is the most likely diagnosis. During the first trimester of pregnancy cholestasis may occur in hiperemesis gravidorum, and in the third trimester of gestation cholestasis of pregnancy should be suspected. A familial history of recurrent cholestasis points to benign recurrent intrahepatic cholestasis. The occurrence of intrahepatic cholestasis in a middle-aged woman is a frequent presentation of primary biliary cirrhosis, whereas primary sclerosing cholangitis should be suspected in young males with inflammatory bowel disease. The presence of vascular spider nevi, ascites, and a history of alcohol abuse should point to alcoholic hepatitis. Neonatal cholestasis syndromes include CMV, toxoplasma and rubinfections or metabolic defects such as cystic fibrosis, α(1)-antitripsin deficiency, bile acid synthesis defects, or biliary atresia. The treatment of cholestasis should include a management of complications such as pruritus, osteopenia and correction of fat soluble vitamin deficiencies. When hepatocellular failure or portal hypertension-related complications occur, liver transplantation should be considered. Copyright .COPYRGT. 2004 Aran Ediciones, S. L.

L3 ANSWER 21 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2004303464 EMBASE Duodenogastric reflux-induced (alkaline) esophagitis.

Richter J.E.. Dr. J.E. Richter, Dept. of Gastroenterology/Hepatology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States. richtej@ccf.org. Current Treatment Options in Gastroenterology Vol. 7, No. 1, pp. 53-58 2004.

Refs: 30.

ISSN: 1092-8472. CODEN: CTOGA7

Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 20040729. Last Updated on STN: 20040729

AB Duodenogastric reflux is the retrograde flow of duodenal contents into the stomach that then mix with acid and pepsin. These agents can reflux into the esophagus (ie, duodenogastroesophageal reflux [DGER]) and cause gastroesophageal reflux disease (GERD) and its complications, including stricture, Barrett's esophagus, and adenocarcinoma of the esophagus. Medical and surgical treatments of DGER can be difficult. Best medical treatment is proton-pump inhibitors, which decrease DGER by inhibiting both gastric acidity and volume, making less gastric contents available to reflux into the esophagus. The addition of the gamma-aminobutyric (GABA(B)) receptor agonist baclofen may further reduce DGER in patients not responding to proton-pump inhibitors. Bile acid-binding agents (aluminum-containing antacids, cholestyramine, sucralfate, urosodeoxycholic acid) have physiologic rationale, but their efficacy is unproven. Prokinetic agents can reduce DGER and its upper gastrointestinal symptoms by promoting increased gastric emptying. In patients with medically refractory symptoms, a Roux-en-Y diversion or duodenal switch operation may be helpful. Copyright .COPYRGT. 2004 by Current Science Inc.

L3 ANSWER 22 OF 59 CAPLUS COPYRIGHT 2007 ACS on STN

2003:319266 Document No. 138:343857 Pharmaceutical formulations and systems for improved absorption and multistage release of active agents. Chen, Feng-Jing; Venkateshwaran, Srinivasan; Krill, Steven L.; Patel, Mahesh V. (USA). U.S. Pat. Appl. Publ. US 2003077297 A1 20030424, 55 pp., Cont.-in-part of U.S. Ser. No. 898,553. (English). CODEN: USXXCO. APPLICATION: US 2002-74687 20020211. PRIORITY: US 1999-258654 19990226; US 1999-345615 19990630; US 1999-447690 19991123; US 2001-800593 20010306; US 2001-877541 20010608; US 2001-898553 20010702.

AB The present invention pertains to pharmaceutical formulations and systems for delivery of active agents, wherein a first fraction of an active agent is suspended in a vehicle and a second fraction of active agent is solubilized in the vehicle, with the suspended fraction representing about 5 weight % to about 80 weight % of the active agent and the second fraction

representing about 20 weight % to about 95 weight % of the active agent. One or more addnl. active agents, which may be fully solubilized, partially solubilized, or suspended, may also be present. The first and second fractions of the active agent may or may not have different release profiles. Generally, a significant fraction of the solubilized drug will release rapidly, providing for rapid onset, while the suspended drug may be formulated for delayed and/or sustained release. A pharmaceutical suspension contained isotretinoin 40, soybean oil 200, Maisine 35-1 100, and Lutrol F68 100 mg.

L3 ANSWER 23 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2003186687 EMBASE Recombinant tissue plasminogen activator for treatment of hepatic veno-occlusive disease following bone marrow transplantation in children: Effectiveness and a scoring system for initiating treatment.
Bajwa R.P.S.; Cant A.J.; Abinun M.; Flood T.J.; Hodges S.; Hale J.P.; Skinner R.. Dr. R. Skinner, Sir J. Spence Inst. of Child Health, Royal Victoria Infirmary, Department of Paediatric Oncology, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, United Kingdom. Bone Marrow Transplantation Vol. 31, No. 7, pp. 591-597 2003.
Refs: 18.
ISSN: 0268-3369. CODEN: BMTRE
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20030529. Last Updated on STN: 20030529

AB Hepatic veno-occlusive disease (HVOD) following bone marrow transplantation is potentially fatal. Criteria for diagnosis and starting treatment are mainly based on adult studies. Recombinant tissue plasminogen activator (rtPA) has been used with variable success. rtPA and heparin were given to 12 children (nine with immunodeficiency, two malignancy, one thalassaemia) with moderate to severe HVOD. Of the 12, 10 responded with a fall in bilirubin concentration; eight survived with complete resolution of HVOD. Four of the five patients with associated multiorgan failure (MOF) died despite rtPA treatment. One child suffered significant, and one minor, bleeding during rtPA treatment. A scoring system for quantifying the severity of HVOD in children is proposed, incorporating the criteria used to diagnose HVOD, risk factors for its development and also parameters reflective of the patient's general condition. This will facilitate early diagnosis and management of those cases which, if not treated promptly, are likely to deteriorate with an adverse outcome. Our experience suggests rtPA and heparin are an effective treatment for HVOD in children, with relatively little toxicity provided therapy is started before MOF develops.

L3 ANSWER 24 OF 59 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2003:577941 The Genuine Article (R) Number: 697XZ. Rational pharmacologic therapy of hepatobiliary disease in dogs and cats. Sartor L L (Reprint); Trepanier L A. Univ Wisconsin, Madison, WI 53706 USA (Reprint). COMPENDIUM ON CONTINUING EDUCATION FOR THE PRACTICING VETERINARIAN (JUN 2003) Vol. 25, No. 6, pp. 432-+. ISSN: 0193-1903. Publisher: VETERINARY LEARNING SYSTEMS, 425 PHILLIPS BLVD #100, TRENTON, NJ 08618 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Treatment of hepatobiliary disease in dogs and cats,often involves the use of multiple drugs for their inflammatory, antifibrotic, cupruretic, hepatoprotectant, antimicrobial, diuretic, procoagulant, or antacid actions. This article reviews the indications for and optimal use of the following agents in the setting of hepatobiliary disorders of dogs and cats: glucocorticoids, azathioprine, colchicine, zinc, D-penicillamine, ursodiol, vitamin E, S-adenosyl-L-methionine, milk thistle (silymarin), carnitine and taurine, antimicrobials, lactulose, spironolactone and other diuretics, vitamin K-1, and gastrointestinal protectants.

L3 ANSWER 25 OF 59 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2003:316107 Document No.: PREV200300316107. Nodular regenerative hyperplasia of the liver: A rare differential diagnosis of cholestasis with response to ursodeoxycholic acid. Faust, D.; Fellbaum, C.; Zeuzem, S.; Dietrich, C. F. [Reprint Author]. Innere Medizin II, Caritas Krankenhaus, Uhlandstrasse 7, 97980, Bad Mergentheim, Germany. Zeitschrift fuer Gastroenterologie, (Maerz 2003) Vol. 41, No. 3, pp. 255-258. print. CODEN: ZGASAX. ISSN: 0044-2771. Language: English.

AB Nodular regenerative hyperplasia of the liver (NRHL) is an uncommon non-malignant finding typically associated with haematological or auto-immune disease. The main clinical symptom is portal hypertension in the absence of underlying liver cirrhosis. The pathogenesis of NRHL remains unknown. We report a case of NRHL with cholestasis and progression to liver insufficiency without any underlying disease and no association with systemic disease or drug intake. Cholestasis and liver function tests improved significantly during treatment with ursodeoxycholic acid (750 mg per day). Based on this case, it may be concluded that treatment with ursodeoxycholic acid might be beneficial in patients with NRHL and progression to liver insufficiency.

L3 ANSWER 26 OF 59 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2003:582123 Document No.: PREV200300571970. DOES URSODEOXYCHOLIC ACID THERAPY ALTER THE PROFILE OF THE LIVER TRANSPLANT RECIPIENT WITH PRIMARY BILIARY CIRRHOSIS?. Gordon, Fiona [Reprint Author]; Muiesan, Paolo [Reprint Author]; Portmann, Bernard C. [Reprint Author]; Knisely, Alex S. [Reprint Author]; O'Donoghue, John [Reprint Author]; Rela, Mohammed [Reprint Author]; Heaton, Nigel D. [Reprint Author]; O'Grady, John G. [Reprint Author]. London, UK. Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. T1607. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract. Language: English.

AB Background Ursodeoxycholic acid (UDCA) therapy in primary biliary cirrhosis (PBC) improves the biochemical profile but may not slow histological progression or influence time to liver transplantation (LT). We aimed to determine whether UDCA therapy modified the clinical profile and/or pathway to liver transplantation. Methods PBC patients' clinical data were obtained from King's College Hospital Liver Transplant Database, comprising of prospectively collected records of all LTs performed between 1st February 1988 to 31st July 2001. UDCA therapy and pathology data were retrieved from case-notes. Patients who received UDCA for >2y pre-LT were used as a subgroup for comparison with those untreated. Wilcoxon signed rank and chi-squared tests were used to compare continuous and discrete variables, respectively. Results Data were available for 168 of 197 patients. Most were female (156; 93%) and the median age of all patients at LT was 54y (range 30-73y). 105 patients received no UDCA, but 63 (38%) received UDCA pre-LT for a mean of 2.3y (range 0.02-7.2y), at a mean dose of 10.2mg/kg/day (range 4.2-15), with 34 patients for >2y. The mean time from diagnosis to LT was 5.8y +/-4.4(SD) in UDCA-untreated patients, compared to 8.9y +/-5.2 in those on UDCA >2y (p=0.002), although the age at LT did not differ between groups. Significantly more UDCA >2y patients received diuretics pre-LT (53%; p=0.01) than those untreated (28%), but numbers with variceal bleeds, maximum encephalopathy scores, Child-Pugh scores and BMI-adjusted explant weights did not differ between groups. Mean serum bilirubin and alkaline phosphatase values at LT of patients on UDCA >2y were significantly lower than of those untreated (p=0.0001, p=0.004, respectively). Mean pre-LT international normalised ratio (INR) was lower in the >2y UDCA group (1.09 +/-0.15) than in untreated patients (1.3 +/-0.5; p=0.003). Platelet count, serum albumin and creatinine did not

differ between groups. Differences in bilirubin, INR and use of diuretics remained significant (p<0.02) when all patients who received UDCA (n=63) were compared with those untreated. Conclusions The results suggest that there may be a shift from the characteristic cholestatic profile of PBC to one more typical of cirrhosis with UDCA therapy. Time from diagnosis to LT appears to have been delayed by UDCA therapy for >2y..

L3 ANSWER 27 OF 59 EMBASE

2003032802 EMBASE [Pseudotumor cerebri caused by oversupplementation of Vitamin A in a cholestatic infant]. PSEUDOTUMOR CEREBRI BEI VITAMIN-A-INTOXIKATION DURCH UBERDOSIERUNG BEI EINEM SAUGLING MIT CHOLESTASE. Ballauff A.; Baumann U.; Rodeck B.. Monatsschrift fur Kinderheilkunde Vol. 150, No. 8, pp. 985-988 2002.
Refs: 11.
ISSN: 0026-9298. CODEN: MOKIAY
Pub. Country: Germany. Language: German. Summary Language: English; German.
Entered STN: 20030207. Last Updated on STN: 20030207

AB Case report. Despite supplementation of fat soluble vitamins children with chronic cholestasis often have low vitamin serum concentrations. Overdosage with oral preparations is rare. We report a 10 month old boy with biliary atresia, who developed pseudotumor cerebri, skin rash and hypercalcemia due to vitamin A intoxication with a highly concentrated vitamin A suspension. After discontinuation of the vitamin A supplementation symptoms vanished quickly but possibly portal hypertension worsened, since the boy experienced the first episode of variceal bleeding. Conclusion. Since vitamin A intoxication induces hepatotoxicity supplementation of vitamin A in cholestatic infants and children should be well controlled. Different concentrations of commercial vitamin A preparations increase the risk of overdosage.

L3 ANSWER 28 OF 59 EMBASE

2003010670 EMBASE Hepatic circulatory diseases associated with chronic myeloid disorders. Poreddy V.; DeLeve L.D.. Dr. L.D. DeLeve, Div. of Gastrointestinal Disease, Univ. S. California Keck Sch. Med., HMR 603, 2011 Zonal Avenue, Los Angeles, CA 90293, United States. deleve@hsc.usc.edu. Clinics in Liver Disease Vol. 6, No. 4, pp. 909-931 2002.
Refs: 129.
ISSN: 1089-3261. CODEN: CLDIF
S 1089-3261(02)00051-X. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20030116. Last Updated on STN: 20030116

AB These liver diseases are diseases of the hepatic circulation. Myeloproliferative disorders are among the most common prothrombotic disorders that lead to Budd-Chiari syndrome and PVT. SOS, previously known as hepatic veno-occlusive disease, is mainly seen in North America and Western Europe as a complication of the conditioning regimen for hematopoietic stem cell transplantation. SOS is caused by damage to SECs, and the initiating circulatory blockage occurs because of the embolism of sinusoidal lining cells. Myeloproliferative disorders are an uncommon cause of NRH, which is believed to be caused by uneven perfusion of the liver at the venous or sinusoidal level. Peliosis hepatis is believed to result from damage to SECs and is seen mainly in immunosuppressed patients, patients with a wasting illness, or patients with a drug toxicity.

L3 ANSWER 29 OF 59 EMBASE

2003109969 EMBASE Hepatobiliary nutrition: History and future. Dudrick S.J.; Kavic S.M.. S.J. Dudrick, Department of Surgery, Bridgeport Hospital, Yale-New Haven Health, 267 Grant Street, Bridgeport, CT 06610, United

States. Journal of Hepato-Biliary-Pancreatic Surgery Vol. 9, No. 4, pp. 459-468 2002.
Refs: 40.
ISSN: 0944-1166. CODEN: JHBSFA
Pub. Country: Japan. Language: English. Summary Language: English.
Entered STN: 20030327. Last Updated on STN: 20030327

AB The liver is a master metabolic gland; consequently, liver disease commonly results in significant malnutrition. Complex metabolic derangements always accompany liver failure, often reflect the magnitude of hepatic insufficiency, and are characterized by accentuated catabolism. Nutritional assessment is problematic in these patients, because many of the usual indicators of nutritional status are altered directly by the hepatic pathophysiology rather than, or in addition to, preexisting or subsequent secondary malnutrition. The objective of nutritional support in patients with liver failure is to provide adequate nutrients to ensure the availability of specific substrates for energy and protein synthesis and for normal hepatocyte survival and function, without inducing or accentuating encephalopathy or otherwise compounding hepatic insufficiency. In the near future, guidelines must be developed for the specific nutritional support of patients with fulminant hepatic failure, cholestatic liver disease, steatosis, and cirrhosis. Currently, work is underway to develop an artificial liver for patients awaiting transplantation; to use genetic engineering technology to provide an alternative source of hepatic tissue; and to test the utility of various intermediary metabolites for hepatobiliary nutrition support. No ideal regimen for nutritional support of all forms of liver failure exists, and this also represents a significant challenge for future basic and clinical investigations. However, it is mandatory to attempt to maintain optimal nutrition in patients with severe liver failure if morbidity and mortality are to be reduced and survival is to be maximized.

L3 ANSWER 30 OF 59 EMBASE

2002372578 EMBASE Gateways to clinical trials. Bayes M.; Rabasseda X.; Prous J.R.. M. Bayes, Prous Science, S.A., P.O. Box 540, 08080 Barcelona, Spain. mbayes@prous.com. Methods and Findings in Experimental and Clinical Pharmacology Vol. 24, No. 7, pp. 431-455 2002.
Refs: 170.
ISSN: 0379-0355. CODEN: MFEPDX
Pub. Country: Spain. Language: English. Summary Language: English.
Entered STN: 20021107. Last Updated on STN: 20021107

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies knowledge area of Prous Science Integrity, the drug discovery and development portal, http://integrity.prous.com. This issue focuses on the following selection of drugs: Adalimumab, aeroDose insulin inhaler, agomelatine, alendronic acid sodium salt, aliskiren fumarate, alteplase, amlodipine, aspirin, atazanavir; Bacillus Calmette-Guerin, basiliximab, BQ-788, bupropion hydrochloride; Cabergoline, caffeine citrate, carbamazepine, carvedilol, celecoxib, cyclosporine, clopidogrel hydrogensulfate, colestyramine; Dexamethasone, diclofenac sodium, digoxin, dipyridamole, docetaxel, dutasteride; Eletriptan, enfuvirtide, eplerenone, ergotamine tartrate, esomeprazole magnesium, estramustine phosphate sodium; Finasteride, fluticasone propionate, fosinopril sodium; Ganciclovir, GBE-761-ONC, glatiramer acetate, gliclazide, granulocyte-CSF; Heparin sodium, human isophane insulin (pyr), Hydrochlorothiazide; Ibuprofen, inhaled insulin, interferon alfa, interferon beta-1a; Lamivudine, lansoprazole, lisinopril, lonafarnib, losartan potassium, lumiracoxib; MAb G250, meloxicam methotrexate, methylprednisolone aceponate, mitomycin, mycophenolate mofetil; Naproxen sodium, natalizumab, nelfinavir mesilate, nemifitide ditriflutate, nimesulide; Omalizumab, omapatrilat, omeprazole, oxybutynin chloride; Pantoprazole sodium, paracetamol, paroxetine, pentoxifylline, pergolide mesylate, permixon, phVEGF-A165, pramipexole hydrochloride, prasterone, prednisone, probucol, propiverine hydrochloride; Rabeprazole

sodium, resiniferatoxin, risedronate sodium, risperidone, rofecoxib rosiglitazone maleate, ruboxistaurin mesilate hydrate; Selegiline transdermal system, sertraline, sildenafil citrate, streptokinase; Tadalafil, tamsulosin hydrochloride, technosphere/Insulin, tegaserod maleate, tenofovir disoproxil fumarate, testosterone heptanoate, testosterone undecanoate, tipifarnib, tolterodine tartrate, topiramate, troglitazone; Ursodeoxycholic acid; Valdecoxib, valsartan, vardenafil, venlafaxine hydrochloride, VX-745.

L3 ANSWER 31 OF 59 EMBASE
2002194898 EMBASE Diseases of the liver: Chronic liver disease. Kennedy P.T.F.; O'Grady J.G.. Dr. P.T.F. Kennedy, Institute of Liver Studies, King's College Hospital, London, United Kingdom. Hospital Pharmacist Vol. 9, No. 5, pp. 137-144 2002.
Refs: 90.
ISSN: 1352-7967. CODEN: HSPMFF
Pub. Country: United Kingdom. Language: English.
Entered STN: 20020620. Last Updated on STN: 20020620
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L3 ANSWER 32 OF 59 CAPLUS
2001:136991 Document No. 134:198075 Triglyceride-free compositions and methods for enhanced absorption of hydrophilic therapeutic agents. Patel, Mahesh V.; Chen, Feng-Jing (Lipocine, Inc., USA). PCT Int. Appl. WO 2001012155 A1 20010222, 113 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18807 20000710. PRIORITY: US 1999-375636 19990817.
AB The present invention relates to triglyceride-free pharmaceutical compns., pharmaceutical systems, and methods for enhanced absorption of hydrophilic therapeutic agents. The compns. and systems include an absorption enhancing carrier, where the carrier is formed from a combination of at least two surfactants, at least one of which is hydrophilic. A hydrophilic therapeutic agent can be incorporated into the composition, or can be co-administered with the composition as part of a pharmaceutical system. The invention also provides methods of treatment with hydrophilic therapeutic agents using these compns. and systems. For example, when a composition containing Cremophor RH40 0.30, Arlacel 186 0.20, Na taurocholate 0.18, and propylene glycol 0.32 g, resp., was used, the relative absorption of PEG 4000 as a model macromol. drug was enhanced by 991%.

L3 ANSWER 33 OF 59 CAPLUS
2001:101167 Document No. 134:168315 Enhancement of bioavailability of peptides with bile salts. Morrison, James Duncan; Lucas, Michael Leslie; Wheeler, Sarah (The University Court of the University of Glasgow, UK). PCT Int. Appl. WO 2001009163 A2 20010208, 28 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-GB2903 20000728. PRIORITY: GB 1999-17793 19990730.
AB The present invention relates to improving and/or increasing the bioavailability of a biol. active substance, such as a peptide. In

particular the present invention relates to the conjugation of the biol. active substance to a bile acid. The conjugated biol. active substance is suitable particularly for oral or parental administration. Illeal administration of 600μg/kg gastrin tetrapeptide conjugated to cholate resulted in a significant mean increase in gastric acid secretion of 1.84 μmol over a 3 h collection period, while no increase in acid secretion was noticed by administration of tetragastrin alone or with sep. cholate.

L3 ANSWER 34 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2001298585 EMBASE Cyclodextrin complexes of salts of acidic drugs. Thermodynamic properties, structural features, and pharmaceutical applications. Redenti E.; Szente L.; Szejtli J.. E. Redenti, R and D Department, Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43100 Parma, Italy. e.redenti@chiesigroup.com. Journal of Pharmaceutical Sciences Vol. 90, No. 8, pp. 979-986 2001.
Refs: 73.
ISSN: 0022-3549. CODEN: JPMSAE
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20010906. Last Updated on STN: 20010906

AB The objective of this mini-review is to summarize the findings concerning the physicochemical properties and the pharmaceutical applications of acidic drugs whose performances have been modified by simultaneous complexation with cyclodextrins and salt formation. Particular attention is paid to the approaches undertaken for increasing the solubility of the drugs by proper choice of the type of counterion analogously to what has been reported for complexes of basic drugs in the presence of hydroxy acids. .COPYRGT. 2001 Wiley-Liss, Inc.

L3 ANSWER 35 OF 59 CAPLUS COPYRIGHT 2007 ACS on STN

2000:645885 Document No. 133:217694 Endotoxin-modulating compounds for therapy of heart failure and cachexia. Anker, Stefan; Coats, Andrew; Volk, Hans-Dieter; Rauchhaus, Mathias; Schumann, Ralf Reiner (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053224 A2 20000914, 74 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2299 20000309. PRIORITY: GB 1999-5300 19990309; GB 1999-5307 19990309; GB 1999-5310 19990309; GB 1999-5314 19990309; GB 1999-5315 19990309.

AB A method of treating, preventing or ameliorating chronic or acute heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids, or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or chronic heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin

(lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. Also disclosed is a method for treating cachexia and wasting syndromes due to diseases other than congestive heart failure.

L3 ANSWER 36 OF 59 CAPLUS COPYRIGHT 2007 ACS on STN
2000:277810 Document No. 132:326056 Systems for oral delivery. Russell-Jones, Gregory John (Biotech Australia Pty. Ltd., Australia). PCT Int. Appl. WO 2000022909 A2 20000427, 32 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IB1872 19991018. PRIORITY: US 1998-PV104827 19981019.

AB A pharmaceutical and a biol. active substance, for oral administration, can be "coated" or "encapsulated" with a carboxylic acid, such that the substance is protected from proteolysis in the stomach and is taken up from the intestine. It is thought that the carboxylic acids coat and protect the active agent from the proteolytic environment of the stomach, allowing the agent to pass safely through the stomach and to be absorbed in the small intestines. The carboxylic acid agent complex can be adopted for oral, nasal, buccal, and transdermal delivery of moderately soluble and even insol. bioactive agents.

L3 ANSWER 37 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
2000278759 EMBASE Serum triglycerides, the liver and the pancreas. Miller J.P.. J.P. Miller, Department of Medicine, S. Manchester Univ. Hosp. NHS Trust, Withington Hospital, Manchester M20 2LR, United Kingdom. Current Opinion in Lipidology Vol. 11, No. 4, pp. 377-382 2000.
Refs: 47.
ISSN: 0957-9672. CODEN: COPLEU
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20000831. Last Updated on STN: 20000831

AB Massive hypertriglyceridaemia associated with fatty liver and abdominal pain or frank pancreatitis (the chylomicronaemia syndrome) is uncommon, but clinically important and underrecognized. It may arise as a result of severe genetic defects in lipolysis or, more commonly, from a moderate primary hypertriglyceridaemia that is exacerbated by a secondary cause. The latter include several drugs, among which the protease inhibitors, used for the treatment of human immunodeficiency virus infection, are increasingly apparent. In the acute situation plasma exchange, fat-free parenteral nutrition and acute insulin treatment, even in nondiabetic persons, may be valuable. A potentially major advance in prophylaxis is the use of high-dose antioxidant therapy, which has been shown to reduce attacks of pancreatitis even in the absence of a reduction in serum triglycerides. Asymptomatic patients with abnormal liver function tests are common in the lipid clinic, and can be a difficult group in which to make management decisions. Among those who are not taking excessive amounts of alcohol, many will have nonalcoholic steatohepatitis. The care of these patients is discussed, but there remains considerable uncertainty regarding their optimum management and prognosis. (C) 2000 Lippincott Williams and Wilkins.

L3 ANSWER 38 OF 59 MEDLINE on STN DUPLICATE 1
1999449169. PubMed ID: 10520859. A pilot study on the hemodynamic effect of short-term ursodeoxycholic acid therapy in patients with stable liver cirrhosis. Baruch Y; Assy N; Weisbruch F; Reisner S A; Rinkevich D; Enat R; Blendis L M; Bomzon A. (Department of Medicine Band

Cardiology, Rambam Medical Center, Haifa, Israel.) The American journal of gastroenterology, (1999 Oct) Vol. 94, No. 10, pp. 3000-4. Journal code: 0421030. ISSN: 0002-9270. Pub. country: United States. Language: English.

AB OBJECTIVE: Total serum bile acid concentrations are elevated in individuals with liver disease. Ursodeoxycholic acid (UDCA) therapy in such patients results in a further significant rise in plasma levels to the extent that it becomes the major circulating bile acid. In laboratory animals, bile acids, such as taurocholic acid, have also been shown to possess a diuretic-like action, as they can promote diuresis, natriuresis, and kaliuresis by inhibiting tubular sodium reabsorption. The aim of the present study was to assess the effect of 1 month's UDCA therapy on cardiovascular function in cirrhotic patients. METHODS: Two groups of patients with cirrhosis were studied, six with primary biliary cirrhosis (PBC) and six with postnecrotic liver cirrhosis (PNC). Cardiovascular function was assessed by determination of blood pressure, heart rate, and by two-dimensional and pulsed Doppler echocardiography. RESULTS: In PBC patients, 1 month's treatment with UDCA significantly reduced diastolic volume without changing systolic, diastolic, and mean blood pressures, heart rate, systolic and stroke volumes, ejection fraction, cardiac output, and systemic vascular resistance. In PNC patients, UDCA significantly reduced cardiac output, with a tendency to reduce left ventricular volumes, without any changes in systolic, diastolic, and mean blood pressures. CONCLUSIONS: UDCA caused reductions in diastolic volume in the PBC patients and cardiac output in the PNC patients. Such reductions are not unlike that seen in individuals treated with diuretics. This diuretic-like action deserves further study, particularly in cirrhotic patients who are also being treated with diuretics or show evidence of cardiac myopathy.

L3 ANSWER 39 OF 59 EMBASE

1999351120 EMBASE Liver transplantation and autoimmunity. Jaeckel E.; Tillmann H.L.; Manns M.P.. Dr. M.P. Manns, Medizinische Hochschule Hannover, Dept. Gastroenterology/Hepatology, Carl Neuberg Str. 1, D-30625 Hannover, Germany. Acta Gastro-Enterologica Belgica Vol. 62, No. 3, pp. 323-329 1999.
Refs: 62.
ISSN: 0001-5644. CODEN: AGEBAX
Pub. Country: Belgium. Language: English. Summary Language: English.
Entered STN: 19991029. Last Updated on STN: 19991029

AB Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent good indications for orthotopic liver transplantation (OLT). While there is effective treatment for AIH (steroids with or without azathioprine) and PBC (ursodeoxycholic acid) no such treatment is currently established for PSC. The need of transplantation can be delayed for AIH and PBC with appropriate therapies, while treatment options for PSC are still controversially discussed. Although the time point for liver transplantation can be roughly estimated for AIH by failure of immunosuppressive therapy and for PBC by prognostic models, the prediction of survival in patients with PSC is more difficult, and further complicated by the risk of developing cholangiocellular carcinoma. Long term (5-year) outcome after liver transplantation approaches 80 to 90% for autoimmune liver diseases unless cholangiocellular carcinoma complicates PSC at the time of OLT. The risk of disease recurrence has been recognised for each of these entities although its clinical relevance is controversial and not exactly determined today. As survival after liver transplantation is steadily increasing, recurrent autoimmune liver disease may become a clinical problem in the future. Recently de novo autoimmune hepatitis after liver transplantation has been reported from several transplant centres, although its importance still needs to be established.

L3 ANSWER 40 OF 59 EMBASE

reserved on STN
2000420082 EMBASE Management of chronic liver disease. Thapa B.R.. B.R. Thapa, Div. of Pediat. Gastro./Nutrition, Postgrad. Inst. of Med. Educ./Res., Chandigarh-160 012, India. Indian Journal of Pediatrics Vol. 66, No. 1 SUPPL., pp. S110-S119 1999.
Refs: 37.
ISSN: 0019-5456. CODEN: IJPEA2
Pub. Country: India. Language: English. Summary Language: English.
Entered STN: 20001214. Last Updated on STN: 20001214
AB Childhood liver disorders have, in general, mode of presentations which are distinct from that in adult population. It is due to varying etiology and natural history of the liver diseases in childhood. Chronic hepatitis B and C can be managed with alpha interferon. Remission rates in children have been reported to be between 20-58%. Recently available lamuvidine has also been used in combination with interferon therapy. Oral chelation therapy and liver transplantation have radically affected the outcome of patients with Wilson's disease. Corticosteroids and immunosuppressive therapy are effective in reducing both morbidity and mortality due to auto-immune hepatitis. Offending carbohydrates are eliminated from the diet of patients with galactosemia and hereditary fructose intolerance. The most important and often neglected component of management of chronic liver diseases in childhood are nutritional management and prompt interventions for ascites, spontaneous bacterial peritonitis, portal hypertension and hepatic encephalopathy. With definitive etiological and histological assessment and institution of specific as well as supportive therapy, children with chronic liver disease can have a prolonged survival with improved quality of life. Several of them can potentially receive the liver transplant as and when it becomes available.

L3 ANSWER 41 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
1999221829 EMBASE Recommendations for management of liver and biliary tract disease in cystic fibrosis. Sokol R.J.; Durie P.R.. Dr. R.J. Sokol, Pediatric Liver Center, Liver Transplantation Programs, Children's Hospital, 1056 East 19th Avenue, Denver, CO 80218, United States. Journal of Pediatric Gastroenterology and Nutrition Vol. 28, No. SUPPL. 1, pp. S1-S13 1999.
Refs: 87.
ISSN: 0277-2116. CODEN: JPGND6
Pub. Country: United States. Language: English.
Entered STN: 19990708. Last Updated on STN: 19990708
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L3 ANSWER 42 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
1999060017 EMBASE Bronchobiliary fistula due to alveolar hydatid disease: Report of three cases. Senturk H.; Mert A.; Ersavasti G.; Tahak F.; Akdogan M.; Ulualp K.. Dr. H. Senturk, Cihangir, Akyol sokak, No: 18-5, Makbul TR-81000, Istanbul, Turkey. American Journal of Gastroenterology Vol. 93, No. 11, pp. 2248-2253 1998.
Refs: 23.
ISSN: 0002-9270. CODEN: AJGAAR
S 0002-9270(98)00508-5. Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 19990304. Last Updated on STN: 19990304
AB Bronchobiliary fistula is a serious complication of echinococcosis of the liver: Surgical and endoscopic treatments have been used successfully in the management of bronchobiliary fistula due to hepatic hydatid cysts. However, very little information exists on the management of bronchobiliary fistula due to alveolar hydatid disease. We report here the efficacy of various potential therapies in three cases.

L3 ANSWER 43 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
1999145830 EMBASE The syndrome of veno-occlusive disease after blood or

marrow transplantation. Carreras E.; Rozman C.. E. Carreras, BMT Section, Hematology Departament, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain. Hematology Vol. 3, No. 4, pp. 303-314 1998.
Refs: 116.
ISSN: 1024-5340. CODEN: HMATFL
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 19990510. Last Updated on STN: 19990510

AB Veno-occlusive disease of the liver (VOD) was originally described in patients who drank infusions made with plants containing pyrrolizidine alkaloids. This disease was characterized, histologically, by a progressive and concentric non-thrombotic narrowing of the lumina of small intrahepatic veins. Later, VOD was related to other pathogens such as alcohol, contraceptives, toxic oil, liver radiation and several antineoplastic drugs. The first case of veno-occlusive disease following bone marrow transplantation (BMT) was reported in 1979. Since then, BMT has proved to be the main cause of VOD which is one of the leading causes of morbidity and mortality after transplant. Clinical manifestations of VOD are very characteristic (jaundice, painful hepatomegaly and fluid retention) but indistinguishable from those produced by other regime-related morphological changes on zone 3 of the liver acinus. For this reason, the term 'syndrome of veno-occlusive disease of the liver' has been adopted to designate the clinical manifestations of conditioning regimen toxicity on this zone. This review focuses on the present knowledge of VOD syndrome after BMT.

L3 ANSWER 44 OF 59 EMBASE

97269679 EMBASE Document No.: 1997269679. Abnormal bile acid metabolism and neonatal hemochromatosis: A subset with poor prognosis. Siafakas C.G.; Jonas M.M.; Perez-Atayde A.R.. Dr. A.R. Perez-Atayde, Department of Pathology, Children's Hospital, 300 Longwood Avenue, Boston, MA 02118, United States. Journal of Pediatric Gastroenterology and Nutrition Vol. 25, No. 3, pp. 321-326 1997.
Refs: 11.
ISSN: 0277-2116. CODEN: JPGND6
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 971002. Last Updated on STN: 971002

AB Background: Inborn errors of bile acid synthesis are newly recognized disorders that may cause the phenotypic appearance of neonatal hepatitis or neonatal cholestasis. Methods: This is a clinicopathologic study of two sets of siblings with cholestatic neonatal liver failure. Results: In 3 of the infants, diagnostic evaluation, including analysis of urinary bile salts, revealed a predominance of 7αhydroxy-3-oxo-4-cholenoic and 7α, 12α- dihydroxy-3-oxo-4cholenoic acids, a pattern consistent with Δ4-3-oxosteroid 5βreductase deficiency, which could be primary or secondary. The fourth infant died before such testing could be carried out. In addition, all 4 infants had histologically disseminated hemochromatosis and met diagnostic criteria for neonatal hemochromatosis. In the 3 infants studied, histologic examination of the liver disclosed giant cell hepatitis with extensive loss of hepatic parenchyma and rapid progression to cirrhosis. Early treatment with ursodeoxycholic acid and cholic acid, previously reported as effective therapy, was given to 2 siblings; it failed to reverse or halt the liver damage, and both infants died. One infant, with the original diagnosis of neonatal hemochromatosis, was treated with a variety of antioxidants and chelation therapy, as recently reported. No improvement was demonstrated, and he went on to liver transplantation. Conclusions: The presentation of Δ4- 3-oxosteroid 5βreductase deficiency as neonatal hemochromatosis may represent a distinct subset of this disorder with an accelerated course, no response to therapy and poor prognosis.

L3 ANSWER 45 OF 59 EMBASE

97170833 EMBASE Document No.: 1997170833. Survival algorithms and outcome analysis in primary biliary cirrhosis. Pasha T.M.; Dickson E.R.. Dr. T.M. Pasha, Division of Gastroenterology, Mayo Clinic, 200 S.W. First St., Rochester, MN 55905, United States. Seminars in Liver Disease Vol. 17, No. 2, pp. 147-158 1997.
Refs: 63.
ISSN: 0272-8087. CODEN: SLDIEE
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 970702. Last Updated on STN: 970702

AB The natural history of primary biliary cirrhosis (PBC) is one of slowly progressive cholestasis with liver damage, development of cirrhosis with its concomitant complications, and death unless the patient undergoes liver transplantation. Natural history studies have identified several variables associated with a decreased survival in patients with PBC. The course of the disease can be divided into three time periods: (1) a presymptomatic phase, probably lasting up to 20 years: (2) a symptomatic phase, with anicteric or mild jaundice, lasting up to 5 to 10 years; and (3) a preterminal or accelerated phase with marked jaundice, lasting up to 2 years. Since the course of the disease is one of slow progression leading to liver failure and death unless liver transplantation intervenes, several investigators have developed statistical models to predict survival. The ability to predict survival for individual patients with PBC has been valuable in the management of these patients, particularly in patient selection and timing of liver transplantation. In addition, survival estimates can be utilized in educating and counseling patients and their families. These models may also be used to evaluate the efficacy of new treatments by comparing natural history survival with the survival achieved by therapeutic effect. Over the past several decades, the natural history models of PBC have been developed in the absence of effective medical therapy. The efficacy of liver transplantation and survival following liver transplantation has now been quantitatively established. Future efforts should be aimed at determining not only survival of patients with primary biliary cirrhosis in the presence of effective medical therapy but also at assessing the quality of life and cost- effectiveness of medical therapy and liver transplantation in the management of patients with primary PBC.

L3 ANSWER 46 OF 59 EMBASE

97170832 EMBASE Document No.: 1997170832. Transplantation for primary biliary cirrhosis. Neuberger J.. J. Neuberger, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, United Kingdom. Seminars in Liver Disease Vol. 17, No. 2, pp. 137-146 1997.
Refs: 56.
ISSN: 0272-8087. CODEN: SLDIEE
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 970702. Last Updated on STN: 970702

AB Primary biliary cirrhosis (PBC) remains one of the commoner indications for orthotopic liver replacement. The two main indications for transplantation are poor quality of life (because of the liver) or end-stage liver disease. A number of prognostic models have identified risk factors indicating poor prognosis, but in practice serum bilirubin greater than 150 μmol/L is used most commonly. Other indications for transplantation include progression of hepatopulmonary syndrome, increasing osteoporosis, evidence of malnutrition, and development of hepatocellular carcinoma. Postoperatively, patients do well. Recurrence of PBC remains controversial, but an increasing number of centers now report that a proportion of patients develop evidence of recurrent disease in the allograft. As yet PBC recurrence remains of little practical importance, although as survival increases beyond 10 years, this may become more relevant.

L3 ANSWER 47 OF 59 MEDLINE on STN

97309587. PubMed ID: 9167002. Effect of niuche-shen-qi-wan on painful muscle cramps in patients with liver cirrhosis: a preliminary report.

Motoo Y; Taga H; Yamaguchi Y; Watanabe H; Okai T; Sawabu N. (Department of Internal Medicine, Kanazawa University, Japan.) The American journal of Chinese medicine, (1997) Vol. 25, No. 1, pp. 97-102. Journal code: 7901431. ISSN: 0192-415X. Pub. country: United States. Language: English.

AB Twelve patients with liver cirrhosis complaining of painful muscle cramps were treated with Niuche-Shen-Qi-Wan (TJ-107). Three patients were at the decompensated state. Muscle cramps disappeared in 4 weeks on the average after oral administration of TJ-107 in all 12 patients. During the period of TJ-107 administration, there was no significant improvement of hepatic function. One patient complained of mild epigastric discomfort after taking TJ-107, but there were no other adverse effects. Our results indicate that TJ-107 is useful for treatment of painful muscle cramps in cirrhotic patients.

L3 ANSWER 48 OF 59 EMBASE

96358518 EMBASE Document No.: 1996358518. Management of hepatic veno-occlusive disease (VOD) in pediatric patients: Retrospective analysis in 6 AIEOP-BMT (Italian Pediatric Hematology Oncology Association-Bone Marrow Transplantation Group) centers.. Miniero R.; Vassallo E.; Soldano S.; Nesi F.; Vai S.; Balduzzi A.; Varotto S.; Dallorso S.; Prete A.; Arcese W.. Dept of Pediatrics, Ospedale Regina Margherita, Piazza Polonia 94,10126 Torino, Italy. Bone Marrow Transplantation Vol. 18, No. SUPPL. 2, pp. 157-159 1996.
ISSN: 0268-3369. CODEN: BMTRE
Pub. Country: United Kingdom. Language: English.
Entered STN: 961218. Last Updated on STN: 961218
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L3 ANSWER 49 OF 59 EMBASE

95247964 EMBASE Document No.: 1995247964. [Internal medicine between uniformity and differentiation]. DIE INNERE MEDIZIN ZWISCHEN EINHEIT UND DIFFERENZIERUNG. Stiefelhagen P.. Innere Abteilung, DRK-Krankenhaus,D-57627 Hachenburg, Germany. Internist Vol. 36, No. 8, pp. 840-844 1995.
ISSN: 0020-9554. CODEN: INTEAG
Pub. Country: Germany. Language: German.
Entered STN: 950912. Last Updated on STN: 950912
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L3 ANSWER 50 OF 59 EMBASE

95161525 EMBASE Document No.: 1995161525. [More on medication adverse effects]. ALGO MAS SOBRE REACCIONES ADVERSAS A MEDICAMENTOS. Saenz Calvo A.; Ausejo Segura M.; Bordas Rodriguez I.; Acuna Aller R.; Gonzalez Alvaro A.; Bellas Beceiro B.. Centro de Salud 'Gomez Acebo', INSALUD, Area/Sector XI, C/Gomez Acebo 20,28021-Madrid, Spain. Atencion Primaria Vol. 15, No. 8, pp. 516-518 1995.
ISSN: 0212-6567. CODEN: ATEPEY
Pub. Country: Spain. Language: Spanish. Summary Language: English; Spanish.
Entered STN: 950627. Last Updated on STN: 950627

AB Objective. To describe adverse drugs effects (ADE) and their frequency in primary care patients. Design. Descriptive and longitudinal study during 1 year (1990). Setting. Urban Health Center. Primary Care. Madrid (Spain). Patients and other participants. 15.483 persons, nine general practitioner and one pharmacist. Interventions. Doctors were invited to register any adverse drug effect they had notice in their patients. Doctors registered information and gave notice to the pharmacist about medicines, dosage and period of administration, clinical manifestations, and improving or not if drug was withdrawal. Measurements and main results. 362 adverse drugs effects were notified, 30,9 ADE per thousand atended patients. 117 principles actives were involved, and 415 clinical manifestations were registered. The more affected patients were women (2/1). The age groups with higher ADE relative frequencies were children

under one year and older people. Conclusions. The absolute frequency of medicines involved in ADE are different to relative frequencies when ADE per thousand prescription units are used. Some of the ADE notified were not referred before in the bibliography, so primary care is a good place to research on pharmacosurveillance.

L3 ANSWER 51 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

95027590 EMBASE Document No.: 1995027590. Hepatic disorders. Features and appropriate management. Aldersley M.A.; O'Grady J.G.. Liver Unit, St James's University Hospital,Leeds LS9 7TF, United Kingdom. Drugs Vol. 49, No. 1, pp. 83-102 1995.
ISSN: 0012-6667. CODEN: DRUGAY
Pub. Country: New Zealand. Language: English. Summary Language: English.
Entered STN: 950209. Last Updated on STN: 950209

AB The spectrum of liver disease is extremely wide, with many of the underlying disorders having acute and chronic presentations. Most of the underlying pathogenetic mechanisms are accounted for by autoimmune disease, viral infection and toxic insult. The management strategy of any liver disease is a combination of treating the symptoms and complications that arise, as well as drug therapies relevant to the specific underlying diagnosis. Encephalopathy, ascites, spontaneous bacterial peritonitis, variceal bleeding and pruritus are the main complications at which drug therapy is directed, although in some cases it represents only 1 aspect of the overall management. Drug therapy per se is largely ineffective in acute liver failure with the possible exception of acetylcysteine, but many drugs are used in the management of the constituent components of this complex medical emergency. Treatments for specific liver conditions are expanding, especially in the areas of autoimmune and viral disease. The increasing availability and success of liver transplantation has tended to change the emphasis of management, and it is often not appropriate to exhaust the treatment options before referring the patient for transplantation. A comprehensive review of all liver disease is beyond the scope of this article, but hopefully the important principles of management and commonly occurring clinical decisions are discussed.

L3 ANSWER 52 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

92012733 EMBASE Document No.: 1992012733. Drug hepatotoxicity in pregnancy. Lewis J.H.. Division of Gastroenterology, Georgetown University Medical Center, Washington, DC, United States. European Journal of Gastroenterology and Hepatology Vol. 3, No. 12, pp. 883-891 1991.
ISSN: 0954-691X. CODEN: EJGHES
Pub. Country: United Kingdom. Language: English.
Entered STN: 920316. Last Updated on STN: 920316
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L3 ANSWER 53 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

91201175 EMBASE Document No.: 1991201175. [Liver and biliary tract disease: Advances in 1990]. LEBER- UND GALLENWEGSERKRANKUNGEN: FORTSCHRITTSBERICHT DES JAHRES 1990. Froehlich F.; Margalith D.; Gonvers J.J.; Fasel J.; Mosimann F.; Lavanchy D.; Bauer J.; Schnegg J.F.; Bauerfeind P.; Frei A.; Guyot J.; Vuillamoz D.; Nicolet M.; Fried M.; Duroux P.; Dorta G.; Bretholz A.; Armstrong D.; Blum A.L.. Abteilung fur Gastroenterologie, PMU/CHUV, Universitat Lausanne, 1011 Lausanne, Switzerland. Therapiewoche Schweiz Vol. 7, No. 6, pp. 390-408 1991.
ISSN: 0256-6869. CODEN: THSCEK
Pub. Country: Germany. Language: German. Summary Language: English.
Entered STN: 911216. Last Updated on STN: 911216
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L3 ANSWER 54 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 2

91074895 EMBASE Document No.: 1991074895. Pathophysiology and clinical basis

of prevention and treatment of complications of chronic liver disease.
Wagner S.; Lautz H.-U.; Muller M.J.; Schmidt F.W..
Gastroenterologie/Hepatologie, Medizinische Hochschule,
Konstanty-Gutschow-Str. 8,3000 Hannover 61, Germany. Klinische
Wochenschrift Vol. 69, No. 3, pp. 112-120 1991.
ISSN: 0023-2173. CODEN: KLWOAZ
Pub. Country: Germany. Language: English. Summary Language: English.
Entered STN: 911216. Last Updated on STN: 911216

AB Chronic liver failure is characterized by the appearance of jaundice, ascites, encephalopthy and/or gasrointestinal bleeding. Acute episodes of hepatic decompensation are fequently precipitated by additional events, e.g. septicaemia, diuretic therapy or excessive protein intake. Identification, correction and treatment of these precipitating factors are first steps in the management of chronic liver failure. Nutritional support is important in the treatment of cirrhotic patients, because malnutrition is one of the major determinants of patient outcome. Management of encephalopathy reduces the appearance of gut-derived nitrogenous toxins and corrects imbalances in amino acid metabolism. Treatment of ascites is salt restriction supported by gentle and incremental administration of diuretics. Ursodesoxycholic acid has become a new and promising modality in the management of cholestatic liver diseases. If conservative therapy fails to recompensate liver function, liver transplantation may be indicated.

L3 ANSWER 55 OF 59 MEDLINE on STN DUPLICATE 3
91184032. PubMed ID: 2081480. Traditional management of liver disorders.
Messner M; Brissot P. (Liver Unit, Pontchaillou Hospital, Rennes, France.
) Drugs, (1990) Vol. 40 Suppl 3, pp. 45-57. Ref: 148. Journal code:
7600076. ISSN: 0012-6667. Pub. country: United States. Language: English.

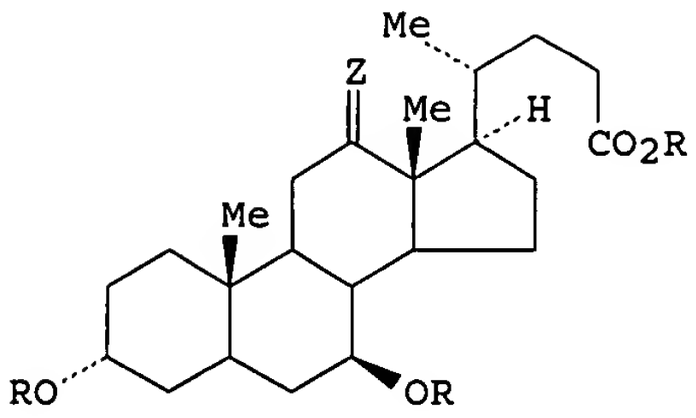
AB Dietary measures have achieved mixed results in the management of liver disorders. Although a high energy diet may shorten the course of viral hepatitis by a relatively small amount, dietary restriction is usually of no benefit in compensated cirrhosis. Restriction of sodium intake to 22 to 60 mol/day leads to resolution of cirrhotic ascites in approximately 20% of patients, and reduces the requirement for diuretics in the remainder. In advanced liver disease, diet plays an important role in the avoidance of portal-systemic encephalopathy (PSE), with the tolerance of most nutrients, most importantly protein, being sharply reduced. Despite the frequent presence of carbohydrate intolerance in liver disease, carbohydrate supplementation may be required to ensure adequate utilisation of the reduced dietary protein intake. Zinc supplementation may also be required in liver cirrhosis to compensate for a deficiency. Bed rest is an important component of the management of acute and chronic liver disorders, together with the avoidance of fatigue. Abstinence from alcohol is required in alcoholic liver disease patients, who should receive parenteral thiamine 100 mg and other vitamin and mineral supplementation as required. Agents acting on the ascending loop of Henle [such as furosemide (frusemide)] or the distal tubule (such as spironolactone) are the diuretics most frequently employed to mobilise ascites in cirrhosis, the latter drug being the more effective in nonazotaemic patients. In the absence of oedema, the diuresis should be restricted to a maximum of 750 ml/day; however, patients with oedema may safely undergo a diuresis of less than or equal to 1.5 L/day. Diuretic therapy is often associated with renal complications, such as azotaemia (usually reversible) and severe hyponatraemia in cirrhotic patients with ascites; spironolactone may produce antiandrogenic adverse effects. Lactulose, used in the treatment of acute and chronic PSE, acts by inhibiting gastrointestinal absorption of ammonia and other toxic nitrogenous substances, and by reducing urea degradation. Other pharmacological treatments, such as branched-chain amino acids and benzodiazepine antagonists have a limited role in the management of PSE. Chronic cholestasis has been treated with cholestyramine and fat-soluble vitamins, whereas ursodeoxycholic acid appears to be a promising agent in the treatment of primary biliary cirrhosis. In chronic hepatitis, the prevention of development of cirrhosis is a primary

treatment goal which has been attempted with variable success using antifibrotic drugs such as penicillamine and colchicine.(ABSTRACT TRUNCATED AT 400 WORDS)

L3 ANSWER 56 OF 59 MEDLINE on STN
86219857. PubMed ID: 2872047. The effect of drugs on bile flow and composition. An overview. Okolicsanyi L; Lirussi F; Strazzabosco M; Jemmolo R M; Orlando R; Nassuato G; Muraca M; Crepaldi G. Drugs, (1986 May) Vol. 31, No. 5, pp. 430-48. Ref: 165. Journal code: 7600076. ISSN: 0012-6667. Pub. country: Australia. Language: English.
AB Many drugs are eliminated via the hepatobiliary route, after biotransformation in the liver. Some of them may affect bile flow and/or the hepatic secretion of biliary lipids such as bile acids, cholesterol and phospholipids. Bile acids are the most potent agents which increase bile flow, especially unconjugated bile acids. Other drugs which increase bile flow include phenobarbitone (phenobarbital), theophylline, glucagon and insulin. In contrast, ethacrynic acid, amiloride, ouabain, oestrogens and chlorpromazine are among those agents which decrease bile flow. Biliary bile acid secretion is altered by a variety of drugs, including cheno- and ursodeoxycholic acids (CDCA and UCDA), the bile acid sequestrants cholestyramine and colestipol, and ethinyloestradiol. The composition of bile can also be altered by drug therapy. Thus, clofibrate increases biliary cholesterol secretion, and reduces bile acid concentrations, without altering biliary phospholipid concentrations. However, other clofibrate derivatives may produce changes of a different pattern, suggesting that the risk of developing gallstones may differ for each derivative. Nicotinic acid and d-thyroxine also increase biliary cholesterol saturation, while CDCA and UDCA reduce biliary cholesterol concentration. The potential consequences of drug-induced changes in bile flow and composition extend to the liver, the gallbladder and the intestine. If adverse effects are to be avoided, further study in this often overlooked area is required.

L3 ANSWER 57 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
85008685 EMBASE Document No.: 1985008685. [Biliary tract drugs. Medical management of gallstones. Choleretics, cholestyramine]. MEDICAMENTS DES VOIES BILIAIRES: TRAITEMENT MEDICAL DE LA LITHIASE BILIAIRE, CHLORETIQUES, COLESTYRAMINE. Erlinger S.. Unite de Recherches de Physiopathologie Hepatique, (INSERM U 24), Hopital Beaujon, 92118 Clichy Cedex, France. Semaine des Hopitaux Vol. 60, No. 38, pp. 2679-2687 1984.
CODEN: SHPAAI
Pub. Country: France. Language: French. Summary Language: English.
Entered STN: 911210. Last Updated on STN: 911210
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L3 ANSWER 58 OF 59 CAPLUS COPYRIGHT 2007 ACS on STN
1983:126470 Document No. 98:126470 High purity ursodeoxycholic acid. Bonaldi, Antonio; Molinari, Egidio (Erregierre S.p.A., Italy). Eur. Pat. Appl. EP 63106 A1 19821020, 20 pp. DESIGNATED STATES: R: AT, BE, CH, DE, FR, GB, LU, NL, SE. (English). CODEN: EPXXDW.
APPLICATION: EP 1982-830083 19820405. PRIORITY: IT 1981-21137 19810414.
GI



I

AB Ursodeoxycholic acid (I; R = H; Z = H2) (II) was prepared from I (R = H, Me3Si; Z = O) by reduction with N2H4 in the presence of an alkaline base and triethylene glycol and subsequent desilylation. II is useful in the treatment of biliary calculi and as an anticholesteremic and diuretic agent (no data).

L3 ANSWER 59 OF 59 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

81073655 EMBASE Document No.: 1981073655. [Unspecific enteritis].
UNSPEZIFISCHE ENTERITIS. Ruppin H.. Med. Klin., Univ. Erlangen-Nurnberg, 8520 Erlangen, Germany. Deutsches Arzteblatt Vol. 77, No. 50, pp. 2959-2969 1980.
CODEN: DEAEB8
Pub. Country: Germany. Language: German.
Entered STN: 911209. Last Updated on STN: 911209
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	186.12	186.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-6.24	-6.24

STN INTERNATIONAL LOGOFF AT 09:28:00 ON 03 MAY 2007

All Search

XP-000971569

I-44

EFFECTS OF URSODEOXYCHOLIC ACID ON INTRAHEPATIC LOCALIZATION OF ENDOTOXIN IN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

K Sasatomi*, K Noguchi, Y Mimura, H Koga, M Oishi, M Harada, S Saitsaka, M Sata, and K Tanikawa
Second Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830, Japan

Aims

Cholestasis may have influence on the intrahepatic kinetics of endotoxin. However, that has not been yet proved. Ursodeoxycholic acid (UDCA) was recently recognized as an effective agent in the treatment of cholestatic liver diseases including primary biliary cirrhosis (PBC). The aim of this study is to clarify the intrahepatic localization of endotoxin and the effect of UDCA on that in patients with PBC.

Materials and Methods

Liver biopsy specimens were obtained from 9 patients with PBC before and after treatment with UDCA. Histologically normal livers were used as controls. Immunohistochemic study was performed using an indirect immunoperoxidase technique with an anti-lipid A of lipopolysaccharide antibody. In addition, the quantitative analysis of lipid A in each cell was carried out using indirect immunofluorescent method with a confocal laser scanning microscope.

Results

Immunoreacts of lipid A markedly accumulated in biliary epithelium from patients with PBC before UDCA treatment. The intensity of staining for lipid A in the liver of patients after UDCA treatment was significantly reduced compared with that in patients before treatment. In Kupffer cells, the fluorescent intensity of lipid A in the liver of patients after UDCA treatment was significantly less than in patients before treatment.

Conclusions

1) In patients with PBC, an accumulation of endotoxin is prominent in biliary pithelium. 2) UDCA treatment apparently reduces an accumulation of endotoxin in biliary epithelium and may also enhance hepatic endotoxin clearance by Kupffer cells. 4) These findings suggest that UDCA treatment may improve the intrahepatic accumulation of endotoxin and may have a beneficial effect on bile duct injury in PBC.

1: Aliment Pharmacol Ther. 1997 Apr;11(2):409-14.

Ursodeoxycholic and tauro-ursodeoxycholic acids for the treatment of primary biliary cirrhosis: a pilot crossover study.

Larghi A, Crosignani A, Battezzati PM, De Valle G, Allocca M, Invernizzi P, Zuin M, Podda M.

Department of Internal Medicine, School of Medicine Ospedale San Paolo, University of Milan, Italy.

BACKGROUND: Results from animal studies and preliminary data from pilot studies in patients with primary biliary cirrhosis suggest that tauro-ursodeoxycholic acid has metabolic properties that may favour its long-term use as an alternative to ursodeoxycholic acid for patients with chronic cholestatic liver diseases. No direct comparison of tauro-ursodeoxycholic and ursodeoxycholic acids have yet been carried out in primary biliary cirrhosis. METHODS: The effects of ursodeoxycholic and tauro-ursodeoxycholic acids were compared in 23 patients with primary biliary cirrhosis according to a crossover design. Both drugs were administered at the daily dose of 500 mg. in a randomly assigned sequence for two 6-month periods separated by a 3-month wash-out period. RESULTS: Serum liver enzymes related to cholestasis and cytolysis consistently improved, as compared to baseline values, during the administration of both ursodeoxycholic and tauro-ursodeoxycholic acids, but no significant difference between these two bile acids was found. Both treatments were well tolerated and no patient complained of side effects. CONCLUSION: In the short-term, tauro-ursodeoxycholic acid appears to be safe and at least as effective as ursodeoxycholic acid for the treatment of primary biliary cirrhosis.

PMID: 9146783 [PubMed - indexed for MEDLINE]

Circulation

American Heart Association.
Fighting Heart Disease and Stroke

(*Circulation.* 1997;96:526-534.)

Articles

Hormonal Changes and Catabolic/Anabolic Imbalance in Chronic Heart Failure and Their Importance for Cardiac Cachexia

Stefan D. Anker, MD; Tuan Peng Chua, MD; Piotr Ponikowski, MD; Derek Harrington, MRCP; Jon W. Swan, MD; Wolfgang J. Kox, MD, PhD; Philip A. Poole-Wilson, MD; ; Andrew J. S. Coats, DM

From Cardiac Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London, UK (S.D.A., T.P.C., P.P., D.H., J.W.S., P.A.P.-W., A.J.S.C.); the Department of Internal Medicine III/Cardiology, Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany (S.D.A.); and the Department of Anesthesiology and Intensive Care Medicine, University Hospital Charité, Humboldt University Berlin, Germany (W.J.K.).

Abstract

Background The role of hormonal and cytokine abnormalities in the development of cardiac cachexia remains obscure.

Methods and Results Healthy control subjects (n=16) and patients with chronic heart failure (CHF), classified clinically as cachectic (8% to 35% weight loss over ≥6 months before study, n=16) or noncachectic (n=37), were assessed for markers of disease severity (maximal oxygen consumption, left ventricular ejection fraction, NYHA functional class). These markers were compared with plasma concentrations of potentially important anabolic and catabolic factors. The degree of neurohormonal activation and catabolic/anabolic imbalance was closely related to wasting but not to conventional measures of the severity of heart failure. Compared with control subjects and noncachectic patients, cachectic patients had reduced plasma sodium and increased norepinephrine, epinephrine (all P <.0001), cortisol, tumor necrosis factor (TNF)-α (both P <.002), and human growth hormone (P <.05). Insulin-like growth factor-1, testosterone, and estrogen were similar in all groups. Insulin was increased only in the noncachectic patients (P <.005 versus control subjects). Dehydroepiandrosterone was reduced in the cachectic patients (P <.02 versus control subjects). Insulin, cortisol, TNF-α, and norepinephrine correlated independently with wasting in CHF (P <.05; multiple regression of these four factors versus percent ideal weight, R^2=.50, P <.0001).

Conclusions Cachexia is more closely associated with hormonal changes in CHF than conventional measures of the severity of CHF. This study suggests that the syndrome of heart failure progresses to cardiac cachexia if the normal metabolic balance between catabolism and anabolism is altered.

Key Words: heart failure • hormones • metabolism • catecholamines • cachexia

Introduction

Chronic heart failure is a heterogeneous syndrome with an overall adverse prognosis. Two particular predictors of adverse prognosis are neurohormonal abnormalities[1] and the development of cachexia.[2]

The syndrome of cardiac cachexia has been recognized for many centuries,[3] but little is known about the mechanisms of the transition from heart failure to cardiac cachexia. Even the definition of cachexia and the characteristics of the cachectic patient are controversial. More than 30 years ago, the pathogenesis of cardiac cachexia was linked to dietary and metabolic factors.[4] In 1990, Levine et al[5] and subsequently others[6 7] showed that TNF-α in plasma is increased in patients with severe heart failure and coexisting cardiac cachexia, as in other wasting disorders. The plasma concentrations of TNF-α partly reflect the local tissue concentration, which is more closely related to muscle wasting.[8] Cytokine activation is a potential causal mechanism for the development of cachexia.

Cardiac cachectic patients suffer from loss of both muscle (ie, protein reserves) and fat tissue (ie, energy reserves), indicative of increased catabolism. An increased resting metabolic rate, regulated primarily by thyroid hormones[9] and catecholamines,[10] has been reported in CHF patients.[11] Cortisol, another catabolic hormone, is also increased in untreated severe congested heart failure patients.[12] Less is known about anabolic metabolism in heart failure. Anand et al[12] found hGH to be greatly increased (≈10-fold) in untreated patients with severe heart failure. To date, these results have not been confirmed by others. Increased plasma insulin levels and insulin resistance occur in patients with CHF.[13]

The neurohormonal hypothesis[1] postulates that heart failure progresses because activated endogenous neurohormonal systems exert a deleterious effect on the heart and circulation. Several studies have found neurohormonal activation to be strongly related to mortality,[14 15 16] but different hormones correlate only weakly with each other.[15] Norepinephrine and plasma renin activity were found not to be related to peak oxygen consumption (peak $\dot{V}O_2$) or LVEF.[16] Left ventricular function, exercise capacity, clinical status, and sympathetic activation were independently related to the progression of CHF.[16]

No previous study has assessed the spectrum of catabolic and anabolic abnormalities in patients with CHF with different degrees of body wasting. We undertook the present study to compare the hormonal changes linked to catabolism and anabolism that occur in the presence and absence of cachexia in patients with CHF. We sought to determine whether neurohormonal changes in CHF were more closely related to the onset of cachexia than to other

conventional markers of the severity of heart failure.

Methods

▲ Top
▲ Abstract
▲ Introduction
▪ Methods
▼ Results
▼ Discussion
▼ References

Patient Population and Characteristics

Measurements were made in 53 male patients with mild to severe CHF and 16 male healthy control subjects of similar age (range, 46 to 68 years). The diagnosis of CHF was based on a history of congestive heart failure of at least 6 months (range, 1 to 20 years) with symptoms, reduced exercise tolerance, cardiomegaly, and objective left ventricular functional impairment. At the time of investigation, all CHF patients were clinically stable. The patients had no clinical signs of acute infection or other primary cachectic states (such as cancer, thyroid disease, or severe liver disease), had no residual signs of peripheral or pulmonary edema, and were studied when free of ascites. No patient was limited by exertional angina. Patients with chronic lung disease, hemodynamically important valve disease, neuromuscular disorders, myocardial infarction within the previous 12 weeks, renal failure, peripheral vascular disease, or excessive alcohol intake were excluded.

Thirty-seven CHF patients were not cachectic (age range, 49 to 75 years). Sixteen CHF patients (age range, 40 to 77 years, P =.08 versus noncachectic patients) had signs of clinical cardiac cachexia. Cardiac cachexia was defined clinically as documented nonintentional dry weight loss of ≥5 kg (all >7.5% of their previous normal weight) over a period of at least 6 months. To exclude patients with intentional weight loss, a second criterion of a body mass index (weight/height^2) of <24 kg/m^2 was used. All cachectic patients also complained of their weight loss. The weight loss amounted to 6 to 30 kg (mean, 11.8±1.5 kg, or 8% to 36% loss of previous body weight) in the preceding 0.75 to 11 years (ie, 6.0±0.9 kg/y).

All subjects performed a maximal treadmill exercise test (modified Bruce protocol, Amis 2000[17]) for estimation of peak $\dot{V}O_2$ (in mL·kg^{-1}·min^{-1}). In patients, the LVEF was measured with radionuclide ventriculography. The protocol was approved by the Ethics Committee of the Royal Brompton Hospital, London. All patients gave written informed consent before the study.

Hormonal Measurements

Blood samples were collected in the morning, between 9 and 10 AM, after a fasting period of ≥12 hours. An antecubital polyethylene catheter was inserted, and after supine rest for at least 20 minutes, 25 mL of venous blood was drawn. After immediate centrifugation, aliquots were stored at -70°C until analysis. IGF-1 (Medgenix; sensitivity, 0.25 ng/mL), hGH (Nichols Institute Diagnostics; sensitivity, 0.02 ng/mL), thyroid stimulating hormone (Bering Diagnostics; sensitivity, 0.3 mU/L), reverse T_3 (Biodata; sensitivity, 0.014 nmol/L), PRA (Biodata SPA; sensitivity, 0.039 ng·mL^{-1}·h^{-1}), and aldosterone (DPC; sensitivity, 16 pg/mL) were measured by radioimmunoassay. Epinephrine and norepinephrine were measured with high-performance liquid chromatography (sensitivity, 0.1 ng/mL for both). TNF-α was measured with an ELISA with a lower limit of detectability of 3.0 pg/mL (Medgenix). This test uses three antibodies directed against distinct epitopes of TNF-α and is not influenced by soluble TNF receptors,[18] ie, it measures the total TNF concentration, bound or unbound. All other parameters (including steroid hormones and insulin) were analyzed by routine analysis in our hospital.

Statistical Analysis

All results are presented as mean±SEM. When ANOVA showed significant differences, Fisher's post hoc test was applied. To analyze relationships between variables, simple linear regression (least-squares method), multivariate analysis, and stepwise regressions were performed (StatView 4.5, Abacus Concepts Inc). To take account of multiple analyses, a probability value of <.01 was considered statistically significant. For multiple and stepwise regression analysis, a value of P <.05 was used to indicate statistical significance. If blood results were below the limit of detectability of a test, the lower limit of detection was recorded. Log-transformed values were used for statistical analysis of basal insulin levels.

Results

▲ Top
▲ Abstract
▲ Introduction
▲ Methods
▪ Results
▼ Discussion
▼ References

Clinical Details

The clinical details and results of the treadmill exercise tests of the patients and control subjects are shown in Tables 1⊞ and 2⊞. The age, body mass index, and percent ideal weight[19] of the 53 patients with CHF were similar to those of the 16 control subjects. The healthy control subjects had a significantly higher treadmill exercise time and exercise capacity. The cachectic and noncachectic patients with CHF had similar peak $\dot{V}O_2$, LVEF, NYHA functional class, disease pathogenesis, drug medication, mean furosemide equivalent dose (106±18 mg versus and 103±19 mg), and duration since onset of heart failure (both patient groups: mean, 5±1 years; median, 3 years) but differed significantly in weight, body mass index, and percent ideal weight (Table 1⊞). Patients with cardiac cachexia (44.9±0.9 g/L) had similar and normal albumin levels compared with control subjects (45.1±0.6 g/L) and noncachectic CHF patients (43.2±0.4 g/L, P <.05 for noncachectic CHF versus control and cachectic subjects). Total protein levels were highest in cachectic CHF patients (72.1±0.9 g/L) compared with noncachectic (69.2±0.7 g/L, P <.05 versus cachectic) and control subjects (66.9±0.7, P =.0004 versus cachectic, P =.053 versus noncachectic subjects). Mean bilirubin levels (ANOVA P =.18) and aspartate aminotransferase activity (ANOVA P =.07, trend for higher levels in noncachectic CHF) did not differ significantly between groups.

View this table: **Table 1.** Characteristics of cCHF and ncCHF Patients Compared With Healthy Control Subjects
[in this window]
[in a new window]

View this table: **Table 2.** Characteristics of 16 Cachectic and 37 Noncachectic CHF Patients
[in this window]
[in a new window]

Hormonal Determinations

All CHF patients. Compared with control subjects, the total group of CHF patients had increased creatinine, PRA, reverse T_3, basal insulin levels, and lowered plasma sodium (all P <.005, Table 3). In addition, trends for increased norepinephrine, epinephrine, and aldosterone as well as for reduced DHEA (P =.01 to .06) were found.

View this table: [in this window] [in a new window] **Table 3.** Results of Hormone Analysis in Healthy Control Subjects and Patients With CHF: Heart Failure Patients Subgrouped by Cachectic State

Cachectic patients. The results for cachectic and noncachectic CHF patients are shown in Table 3. The plasma sodium concentration was decreased, and epinephrine, norepinephrine, cortisol, and TNF-α were substantially increased in cachectic CHF patients (all P ≤.0002 versus noncachectic CHF patients, all P ≤.0015 versus control subjects). In cachectic patients, aldosterone and hGH were increased compared with noncachectic patients (both P <.01), and aldosterone, PRA, reverse T_3, and creatinine were increased compared with control subjects (all P <.005). Individual values varied from normal to greatly elevated levels in the cachectic patients. There were trends for increased hGH and reduced DHEA in cachectic patients compared with control subjects (both .01<P <.05). This trend reached statistical significance for DHEA, when the cachectic patients with <85% of normal weight (n=9; mean, 6.4±1.5 nmol/L) were compared with the control subjects (P =.008).

Noncachectic patients. Compared with control subjects, the noncachectic patients had significantly increased insulin (P <.005) and trends toward increased creatinine, reverse T_3, and PRA (all .01<P <.05). The noncachectic patients had levels of epinephrine, norepinephrine, TNF-α, cortisol, and hGH similar to the control subjects (all P >.20).

No significant differences between groups were seen for albumin, potassium, IGF-1, thyroid-stimulating hormone, testosterone, or estrogen (ANOVA P >.05 for each).

Relation between hGH and IGF-1. Because IGF-1 is the anabolic mediator of hGH, the relation between the two hormones was studied. The IGF-1/hGH ratio was approximately four times higher in noncachectic CHF patients and control subjects than in cachectic subjects. Because this ratio has a skewed distribution, the log-transformed ratios were compared statistically (control subjects, 2.89±0.25; noncachectic, 3.00±0.16; cachectic, 2.03±0.22, P =.014 versus control subjects and P =.0014 versus noncachectic subjects).

Predictors of Muscle Wasting

Weight loss. Only in cachectic patients could the documented weight loss be correlated with physiological measures and humoral parameters. Significant correlates of weight loss (in kilograms) in simple regression analysis were TNF-α (r =.78, P =.0003), reverse T_3 (r =.61, P =.012), peak $\dot{V}O_2$ (r =-.54, P =.032). Independent predictors of documented weight loss in a multivariate model with age, TNF-α, reverse T_3, cortisol, norepinephrine, and insulin were TNF-α (P =.006) and reverse T_3 (P =.044). Predictors of documented weight loss in a stepwise regression model with age, peak $\dot{V}O_2$, and 12 humoral factors were TNF-α in the first step (F value, 22.24; P <.001) and testosterone in the second step (F value, 4.13; P <.025). Similar results were found when the weight loss was normalized for the previous normal weight (TNF-α versus percent weight loss, r =.80, P =.0002). When the derived measure of the ratio of IGF-1 and hGH was analyzed together with TNF-α and testosterone, these three variables predicted 83.5% of the variation of the documented weight loss (in kilograms) and 84.7% of the variation of the relative weight loss (in percent) in 16 cachectic CHF patients (see Table 4). It is important to note that neither testosterone nor log IGF-1/hGH significantly correlated with the body mass index or measures of weight loss but that both became (independently of each other) important after adjustment for the effect of TNF.

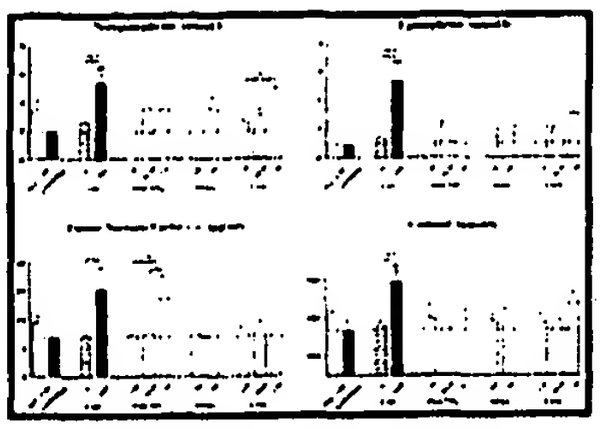
View this table: [in this window] [in a new window] **Table 4.** Stepwise and Multiple Regression Analysis of the Association Between TNF-α and Testosterone Levels and the Ratio of IGF-1 and hGH Levels (log IGF-1/hGH) on Documented Weight Loss in 16 Cachectic CHF Patients

Ideal body weight. In Table 5, we present the results of correlation analysis for percent ideal weight. Significant correlates of lower weight (ie, percent ideal weight) in 53 CHF patients were epinephrine, cortisol, norepinephrine, TNF-α, log IGF-1/hGH (P <.001), hGH, and basal insulin (both P <.01) but also reverse T_3 (r =-.34), age (r =-.32), and plasma sodium (r =-.31, all P <.05). Predictors of reduced weight in a multivariate model with these 10 parameters were insulin (P =.036) and to a lesser extent cortisol (P =.10), TNF-α (P =.13), and norepinephrine (P =.20). In a smaller multivariate model with only these four humoral factors, it was found that they predicted weight changes independently of each other in our CHF population: insulin and cortisol (both P <.01), TNF-α, and norepinephrine (both P <.05). Stepwise regression showed that, one after another, these factors contributed significantly to the variation of the weight (all four factors together versus percent ideal weight: R^2=.501, P <.0001). The inclusion of testosterone did not change the principal outcome of the multivariate and the stepwise regression models for percent ideal weight.

View this table: [in this window] [in a new window] **Table 5.** Relation Between Age and Resting Humoral Factors and Body Weight (Measured in % Ideal Body Weight): Results of Univariate Linear Regression Analysis

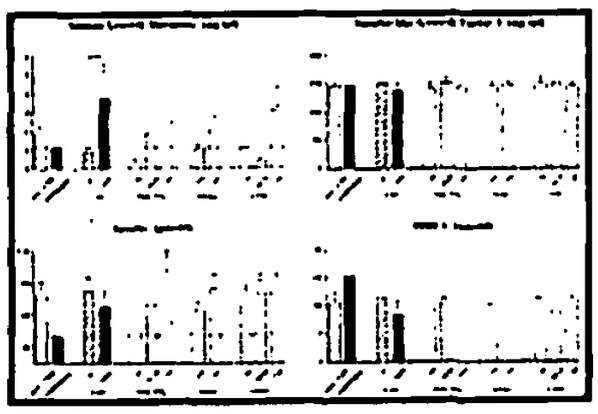
Influence of Other Clinical Markers

To investigate the best discriminators for explaining the variations in the degree of neurohormonal activation, patients were subgrouped according to peak $\dot{V}O_2$, NYHA functional class, and LVEF. The main results of these analyses are presented in Fig 1 (catecholamines, cortisol, and TNF-α) and Fig 2 (hGH, IGF, insulin, DHEA) compared with the earlier grouping according to the cachectic state.



View larger version (32K):
[in this window]
[in a new window]

Figure 1. Levels of catabolic factors (norepinephrine, epinephrine, cortisol, and TNF-α) in 16 healthy control subjects and 53 patients with CHF. Heart failure patients were subgrouped by cachectic state (noncachectic [nc], n=37; cachectic [cach], n=16), peak $\dot{V}O_2$ (<14 [n=17] vs 14 to 20 [n=24] vs >20 mL·kg^{-1}·min^{-1} [n=12]), functional NYHA class (class 1/2 [n=16] vs class 3/4 [n=37]), and LVEF (<20 [n=24] vs 20 to 35 [n=17] vs >35% [n=12]). Probability values for Fisher's test are given if ANOVA showed significant intergroup variation. Data are mean±SEM. *P <.05 for intergroup comparison; ***P <.001 for intergroup comparison; ●P <.05 vs control subjects; ●●P <.01 vs control subjects; and ●●●P <.001 vs control subjects.



View larger version (34K):
[in this window]
[in a new window]

Figure 2. Levels of anabolic hormones (hGH, IGF-1, insulin, DHEA) in 16 healthy control subjects and 53 patients with CHF. Data are mean±SEM. Subgrouping of heart failure patients and statistical presentation as in legend of Fig 1.

Peak $\dot{V}O_2$. The CHF patients were stratified according to their peak $\dot{V}O_2$ (<14, 14 to 20, and >20 mL·kg^{-1}·min^{-1}). The only significant intergroup difference was observed for creatinine (P <.01 for peak $\dot{V}O_2$ <14 [146±14 μmol/L] versus peak $\dot{V}O_2$ 14 to 20 mL·kg^{-1}·min^{-1} [117±12 μmol/L]).

NYHA class. The influence of clinical status as assessed by the functional NYHA classification was analyzed comparing patients in NYHA class 1 or 2 with patients in NYHA class 3 or 4. No significant alterations at the P <.01 level could be detected for any of the hormones studied.

LVEF. Stratification of patients according to LVEF was studied (<20% versus 20% to 35% versus >35%). Significant intergroup differences were found only for aldosterone (LVEF <20% [989±177 pmol/L] versus 20% to 35% [462±66 pmol/L] and versus >35% [456±78 pmol/L], both P <.01).

It is important to note that for only 2 of the 17 humoral factors (aldosterone and creatinine) were comparisons between groups of CHF patients divided according to NYHA class, LVEF, or peak $\dot{V}O_2$ significant at the P <.01 level. If the more stringent Bonferroni correction was applied (17 humoral parameters analyzed; P <.05/17, or .00294, considered significant), no significant difference could be found for any comparison. In contrast, the classification into cachectic and noncachectic patients led to substantial differences in many neurohormonal and anabolic/catabolic factors (Table 3, Figs 1 and 2). The results of regression analysis of several hormones and TNF-α versus markers of disease severity in the CHF patients are shown in Table 6 compared with the relation to percent ideal weight.

View this table:
[in this window]
[in a new window]

Table 6. Univariate Regression Coefficients for the Relation Between Hormones and Cytokines vs Conventional Markers of Severity of CHF and Normalized Body Weight in 53 Patients With CHF

Discussion

▲ Top
▲ Abstract
▲ Introduction
▲ Methods
▲ Results
• Discussion
▼ References

The major finding of this study is that cachexia is associated with hormonal changes in CHF and more conventional measures of severity of CHF are not. Patients with cardiac cachexia demonstrate severe hormonal changes consistent with sympathetic activation and catabolic/anabolic imbalance. These hormonal changes are most clearly demonstrated when patients are subgrouped on the basis of their cachectic status. Several humoral factors are independently related to weight changes in these patients. Subgrouping by cachexia is more predictive of the neurohormonal status than conventional classifications of severity of CHF. These findings suggest that the catabolic/anabolic disturbance leading to cachexia and the neurohormonal activation are related and of greater importance than the degree of hemodynamic or functional disturbance. Much of the variability in the association of conventional measures of the severity of heart failure and neurohormonal activation, and indeed much of the neurohormonal activation itself, is attributable to cachexia and to the small group of patients with cachexia who are included in many studies.

Definition of Cardiac Cachexia

No agreed-upon definition of cachexia exists, but body fat estimation, anthropometric measurements, predicted percent ideal mass, weight/height index, body mass index, serum albumin, and cell-mediated immunity changes, and especially a weight loss of >10% of the previous normal (ie, "usual") weight, have all been used. Patients have been classified as "malnourished" when the body fat content was <22% in women and <15% in men or when the

percentage of ideal weight was <90%.[20] Other groups have defined CHF patients prospectively as "cachectic" when the body fat content was <29% (women) or <27% (men)[6] or when the body weight was <85%[5] or even <80% of ideal.[21]

The development of the cachectic state in CHF could be demonstrated by a longitudinal study in which body weight is measured in a nonedematous state. Including the weight loss as a criterion excludes patients who are constitutionally underweight. Equally, patients initially overweight may be mistakenly classified as cachectic. We used a broad definition of "clinical cardiac cachexia," ie, documented weight loss of ≥5 kg over a period of ≥6 months and a body mass index of ≤24 kg/m^2 observed in patients with CHF without signs of other primary cachectic states. All patients had a weight loss of >7.5% of their previous normal nonedematous body weight. A body mass index of <24 excludes previously obese patients who could merely have lost weight as a consequence of intentional dieting. Because all such definitions are arbitrary, it is important to note that our findings do not differ when the analysis uses different cutoff values for defining cachexia, such as >10% premorbid weight loss (14 patients) or weight loss ≥5 kg and weight <85% of ideal (9 patients).

Development of Cardiac Cachexia

In 1964, Pittman and Cohen,[4] writing about the pathogenesis of cardiac cachexia, stressed the importance of cellular hypoxia to the initiation of less efficient intermediary metabolism, thereby increasing catabolism (protein loss) and reducing anabolism. In addition, they suggested anorexia and increased basal metabolic rate to be the result of a lack of oxygen. Buchanan and colleagues[22] found anorexia that was reversible after mitral valve replacement to be the cause of the cachexia in 11 patients. Neither malabsorption nor cellular hypoxia was of importance. Starvation and anorexia in otherwise healthy persons led to a preferential loss of fat tissue. A study in 27 CHF patients (mean weight, 21% lower than normal)[23] failed to show fat tissue loss but documented an average total body potassium decrease of 35% (a measure of lean tissue independent of body water content). Another study[11] demonstrated increased resting metabolic rates in CHF patients compared with control subjects, a feature of interest given that resting metabolic rate has been shown to correlate with increasing concentrations of catecholamines,[10] and we have now shown catecholamines to be increased markedly in cardiac cachexia. Physical inactivity and deconditioning have been suggested to be important for the muscle atrophy observed in many CHF patients,[24] but recent histological evidence suggests that the atrophy in states of reduced activity is different from the muscle atrophy observed in CHF.[25,26] This is also supported by the finding that the duration of heart failure was not different in cachectic and noncachectic patients. In contrast to the commonly held belief, albumin levels were not decreased in the cachectic patients. This would argue against a major contribution of gastrointestinal malabsorption or liver synthetic dysfunction in these patients.

Catabolic Factors

In the 1930s, the existence of an unexplained pyrogen as a product of anaerobic metabolism in cases of fever in heart failure was suggested.[27] In 1990, Levine and colleagues[5] reported that TNF-α is increased in patients with cardiac cachexia. Increased TNF-α has been confirmed by others[6,7] and in the present study. TNF-α is one of the key cytokines important to the development of catabolism. Animal experiments have shown that the implantation of TNF-α–producing tumor cells in skeletal muscle causes muscle wasting, whereas TNF-α–producing cells in the brain caused marked anorexia.[8] This shows that increased levels of TNF-α may indeed play a causative role in the development of cachexia but also that the site of the production and action of TNF-α modifies its effect. The failing human heart can directly produce TNF-α.[28] Whether this relates to the development of cardiac or general muscle wasting is not known. The new finding of this study is that cytokine activation is only one pathway of those closely related to the degree of wasting and that after adjustment for the influence of TNF, an indirect measure of growth hormone resistance (ie, log IGF-1/hGH) and testosterone levels also seem to be of importance.

Many studies have investigated catecholamine levels in CHF patients. Plasma norepinephrine may reflect overall sympathetic activity,[29] and both norepinephrine and epinephrine can cause a catabolic metabolic balance.[10,30] Since the original observation in 1962 of increased catecholamines in CHF,[31] no study has investigated catecholamine levels specifically in cachectic CHF patients. Only cachectic CHF patients showed markedly increased norepinephrine and epinephrine levels, with noncachectic CHF patients having near-normal levels (Table 3). None of the three other methods of stratifying the 53 CHF patients revealed significant changes between different groups of CHF patients. This suggests a specific association between cachexia and sympathetic activation in CHF. Another hormone considered to be part of the general stress response with a catabolic action is cortisol.[32] In untreated severe CHF patients, Anand et al[12] demonstrated a 2.5-fold increase of cortisol, probably due to an increase in the release of adrenocorticotropic hormone.[33] The cachectic patients in our study had a 2-fold increase. No other subgrouping of the CHF patients revealed any significant effect on mean cortisol levels.

Anabolic Hormones

We studied several anabolic hormones such as sex steroids (testosterone, DHEA, and estrogen), hGH, IGF-1, and insulin. We looked for counterregulatory increases of anabolic factors in cachectic CHF patients. Only hGH was increased (Table 3). Anand et al[12] demonstrated such an increase of hGH in untreated patients with severe CHF. The role of hGH in CHF is unclear, because it has both direct and indirect effects. Directly, it acts on lipid metabolism (catabolic), but normally its major (anabolic) effect is indirect via the somatomedins (the main hGH-dependent somatomedin is IGF-1). By this mechanism, hGH acts in an insulin-like manner (ie, anabolic on cell proliferation and protein synthesis) and is opposed to the actions of cortisol.[34] Because the increase in hGH in our cachectic patients was not accompanied by an increase of IGF-1, this suggests the presence of growth hormone resistance, and via its direct action, hGH could then even promote increased catabolism. These findings merit further investigation.

Insulin is considered to be the most powerful physiological anabolic hormone. In stable CHF patients, we have previously described the development of insulin resistance along with increases of basal insulin levels.[13] Cardiac cachectic patients showed slightly reduced insulin levels compared with noncachectic patients but increased levels compared with normal control subjects. There were no significant changes of testosterone or estradiol levels. Interestingly, the mean concentration of the anabolic hormone DHEA was reduced in all heart failure patients as well as in the subgroup of cachectic CHF patients compared with control subjects (both trends with P <.05, Table 3).

Catabolic/Anabolic Imbalance

In cachectic CHF patients, factors that are acting to increase protein and fat tissue degradation and stimulate energy production are increased (norepinephrine, epinephrine, cortisol, TNF-α), whereas anabolic factors either respond inadequately to cachexia (DHEA is reduced in most severely cachectic patients; testosterone does not increase) or appear to develop a resistance syndrome (growth hormone). This suggests that the syndrome of cardiac cachexia is characterized by a severe catabolic/anabolic imbalance in favor of catabolic metabolism, which may be a valid target for novel therapeutic interventions. It is unlikely that any single physical or biochemical disorder causes cardiac cachexia in all patients.

We found no marked reduction of albumin levels in our cachectic patients compared with control subjects, which is to some degree unexpected. The diuretic doses were similar in the two patient groups. The liver function of the cachectic and noncachectic CHF patients appeared to be normal. Therefore, we do not believe that the albumin results are likely to reflect impaired hepatic albumin synthesis accompanied by decreased blood volume due to diuretics. Taken

together, the results argue against a major impact of anorexia and starvation in the majority of these cachectic CHF patients.

Limitations

The present study is a cross-sectional study. The differences have been described, but changes over time have not been shown. The proof of causality requires a prospectively designed longitudinal study. For clarity of presentation, we subdivided patients into categories of increasing severity. This was arbitrary, but similar conclusions can be drawn when the classification of severity was analyzed using all individual points in regression analysis. Table 5 shows strong inverse relationships between several increased hormones and TNF and reduced body weight that cannot be found with conventional severity markers (Table 6). One of the strengths of the present investigation is also one of its limitations: the multiple biochemical investigations. We chose 17 humoral factors that characterize heart failure severity, catabolism, or anabolism and investigated 69 subjects in three groups. Necessarily, we performed many statistical tests. We reduced the level of significance by a factor of 5 from 5% to 1%, protecting against chance findings. Because the results have a physiological explanation, we believe that our results are indicative. Finally, many other interesting and possibly causally important factors were not included in our analysis, for example, prostaglandins, interferons, interleukins and soluble TNF receptors, adhesion molecules, hGH- and IGF-binding proteins, sex hormone–binding globulin, atrial natriuretic peptide, and endothelins. This study was performed only in male CHF patients, because sex steroid levels are not comparable in men and women. Therefore, it is difficult to draw conclusions on the development of cardiac cachexia in women, but we have no reason to believe that the general pattern of stress responses and immune activation would be different in women. We are aware that several hormones intercorrelate, and this may influence the outcome of the statistical analysis. For instance, it is known that cytokines may inhibit testosterone synthesis,[35] which suggests an inverse relationship between these two parameters. This was not found when our population was analyzed as a whole, but it is indeed present in the subgroup of cachectic patients (data not presented).

Conclusions

Catabolic/anabolic disturbance and hormonal activation are relevant to the development of cardiac cachexia. In an extension of the neurohormonal hypothesis,[1] which postulates that heart failure progresses because activated endogenous neurohormonal systems exert a deleterious effect on the heart and circulation, this study suggests that the syndrome of heart failure progresses to cardiac cachexia when the normal metabolic balance of catabolism and anabolism is altered.

Selected Abbreviations and Acronyms

CHF	=	chronic heart failure
hGH	=	human growth hormone
IGF-1	=	insulin-like growth factor-1
LVEF	=	left ventricular ejection fraction
PRA	=	plasma renin activity
T_3	=	triiodothyronine
TNF	=	tumor necrosis factor

Acknowledgments

Dr Anker was supported by a grant from the Ernst und Bertha Grimmke–Stiftung, Düsseldorf, Germany, and by a fellowship from the European Society of Cardiology. Cardiac Medicine, National Heart and Lung Institute, Imperial College School of Medicine is supported by the British Heart Foundation and the Viscount Royston Trust.

Footnotes

Reprint requests to Dr Stefan Anker, Cardiac Medicine, National Heart and Lung Institute London, Imperial College School of Medicine, Dovehouse St, London SW3 6LY, UK.

Received August 22, 1996; revision received February 4, 1997; accepted February 11, 1997.

References

▲ Top
▲ Abstract
▲ Introduction
▲ Methods
▲ Results
▲ Discussion
• References

1. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol.* 1992;20:248-254.[Medline]
2. Abel RM, Fischer J, Buckley MJ, Barnett GO, Austen WG. Malnutrition in cardiac surgical patients. *Arch Surg.* 1976;111:45-50.[Medline]
3. Katz AM, Katz PB. Diseases of heart in works of Hippocrates. *Br Heart J.* 1962;24:257-264.
4. Pittman JG, Cohen P. The pathogenesis of cardiac cachexia. *N Engl J Med.* 1964;271:403-409.
5. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med.* 1990;323:236-241.[Abstract]
6. McMurray J, Abdullah I, Dargie HJ, Shapiro D. Increased concentrations of tumor necrosis factor in `cachectic' patients with severe chronic heart failure. *Br Heart J.* 1991;66:356-358.[Abstract]
7. Dutka DP, Elborn JS, Delamere F, Shale DJ, Morris GK. Tumor necrosis factor a in severe congestive cardiac failure. *Br Heart J.* 1993;70:141-143.[Abstract]
8. Tracey KJ, Morgello S, Koplin B, Fahey TJ III, Fox J, Aledo A, Manogue KR, Cerami A. Metabolic effects of cachectin/tumor necrosis factor are modified by site of production: cachectin/tumor necrosis factor-secreting tumor in skeletal muscle induces chronic cachexia, while implantation in

brain induces predominantly acute anorexia. *J Clin Invest.* 1990;86:2014-2024.[Medline]
9. Himms-Hagen J. Thyroid hormones and thermogenesis. In: Girardier L, Stock MJ, eds. *Mammalian Thermogenesis* . London, UK: Chapman & Hall; 1983:141-177.
10. Poehlman ET, Danforth E. Endurance training increases metabolic rate and norepinephrine appearance rate in older individuals. *Am J Physiol.* 1991;261:E233-E239.[Medline]
11. Poehlmann ET, Scheffers J, Gottlieb SS, Fisher ML, Vaitekevicius P. Increased resting metabolic rate in patients with congestive heart failure. *Ann Intern Med.* 1994;121:860-862.[Medline]
12. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin: studies on body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation.* 1989;80:299-305.[Abstract]
13. Swan JW, Walton C, Godsland IF, Clark AL, Coats AJS, Oliver MF. Insulin resistance in chronic heart failure. *Eur Heart J.* 1994;15:1528-1532.[Medline]
14. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector TS. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med.* 1984;311:819-823.[Abstract]
15. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L, for the CONSENSUS Trial Study Group. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. *Circulation.* 1990;82:1730-1736.[Abstract]
16. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A, for the V-HeFT VA Cooperative Studies Group. Plasma norepinephrine, plasma renin activity, and congestive heart failure: relations to survival and the effects of therapy in V-HeFT II. *Circulation* . 1993;87(suppl VI):VI-40-VI-48.
17. Volterrani M, Clark AL, Ludman PF, Swan JW, Adamopopoulos S, Piepoli M, Coats AJS. Predictors of exercise capacity in chronic heart failure. *Eur Heart J.* 1994;15:801-809.[Medline]
18. Engelberts I, Stephens S, Francot GJM, Van der Linden CJ, Buurman WA. Evidence for different effects of soluble TNF-receptors on various TNF measurements in human biological fluids. *Lancet.* 1991;338:515-516.
19. National Center for Health Statistics. Weight by height and age for adults 18-74 years: United States 1971-1974. Vital and health statistics. Series 11. No. 208. Washington DC: Government Printing Office; 1979. DHEW publication PHS 79-1656.
20. Carr JG, Stevenson LW, Walden JA, Heber D. Prevalence and hemodynamic correlates of malnutrition in severe congestive heart failure secondary to ischemic or ideopathic dilated cardiomyopathy. *Am J Cardiol.* 1989;63:709-713.[Medline]
21. Otaki M. Surgical treatment of patients with cardiac cachexia: an analysis of factors affecting operative mortality. *Chest.* 1994;105:1347-1351.[Abstract]
22. Buchanan N, Keen RD, Kingsley R, Eyberg CD. Gastrointestinal absorption studies in cardiac cachexia. *Intensive Care Med.* 1977;3:89-91.[Medline]
23. Thomas RD, Silverton NP, Burkinshaw L, Morgan DB. Potassium depletion and tissue loss in chronic heart disease. *Lancet.* 1979;310:9-11.
24. Mancini DM, Walter G, Reichek N, Lenkinski R, McCully KK, Mullen JL, Wilson JR. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation.* 1992;85:1364-1373.[Abstract]
25. Vescovo G, Serafini F, Facchin L, Tenderini P, Carraro U, Della Libera L, Catani C, Ambrosio GB. Specific changes in skeletal muscle myosin heavy chains composition in cardiac failure: differences compared with disuse atrophy as assessed on microbiopsies by high resolution electrophoresis. *Heart.* 1996;76:337-343.[Abstract]
26. Simioni A, Long CS, Yue P, Dudley GA, Massie BM. Heart failure in rats causes changes in skeletal muscle phenotype and gene expression unrelated to locomotor activity. *Circulation* . 1995;92(suppl I):I-259. Abstract.
27. Cohn AE, Steele JM. Unexplained fever in heart failure. *J Clin Invest.* 1934;13:853-868.
28. Torre-Amione G, Kapadia S, Lee J, Durand J-B, Bies RD, Young JB, Mann DL. Tumor necrosis factor-α and tumor necrosis factor receptors in the failing human heart. *Circulation.* 1996;93:704-711.[Abstract/Full Text]
29. Goldstein DS. Plasma norepinephrine as an indicator of sympathetic neural activity in clinical cardiology. *Am J Cardiol.* 1981;48:1147-1154.[Medline]
30. Landsberg L, Young JB. Catecholamines and the adrenal medulla. In: Wilson JD, Foster DW, eds. *Williams Textbook of Endocrinology* . Philadelphia, Pa: WB Saunders; 1992:621-705.
31. Chidsey CA, Harrison DC, Braunwald E. The augmentation of plasma norepinephrine response to exercise in patients with congestive heart failure. *N Engl J Med.* 1962;267:650-654.
32. Orth DN, Kovacs WJ, DeBold CR. The adrenal cortex. In: Wilson JD, Foster DW, ed. *Williams Textbook of Endocrinology* . Philadelphia, Pa: WB Saunders; 1992:489-619.
33. Nicholls MG, Espiner EA, Donald RA, Hughes H. Aldosterone and its regulation during diuresis in patients with gross congestive heart failure. *Clin Sci Mol Med.* 1974;47:301-315.[Medline]
34. Underwood LE, Van Wyk JJ. Normal and aberrant growth. In: Wilson JD, Foster DW, ed. *Williams Textbook of Endocrinology* . Philadelphia, Pa: WB Saunders; 1992:1079-1138.
35. Xiong Y, Hales DB. The role of tumor necrosis factor-α in the regulation of mouse Leydig cell steroidgenesis. *Endocrinology.* 1993;132:2438-2444.[Abstract]

This article has been cited by other articles:

- Bales, C. W., Ritchie, C. S. (2002). SARCOPENIA, WEIGHT LOSS, AND NUTRITIONAL FRAILTY IN THE ELDERLY. *Annu. Rev. Nutr.* 22: 309-323 [Abstract] [Full Text]
- Benedini, S., Fiocchi, R., Battezzati, A., Scifo, P., Sereni, L. P., Gamba, A., Mammana, C., Del Maschio, A., Perseghin, G., Luzi, L. (2002). Energy Metabolism in Diabetic and Nondiabetic Heart Transplant Recipients. *Diabetes Care* 25: 530-536 [Abstract] [Full Text]
- Weber, K. T. (2001). Aldosterone in Congestive Heart Failure. *N Engl J Med* 345: 1689-1697 [Full Text]
- EID, A. A., IONESCU, A. A., NIXON, L. S., LEWIS-JENKINS, V., MATTHEWS, S. B., GRIFFITHS, T. L., SHALE, D. J. (2001). Inflammatory Response and Body Composition in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 164: 1414-1418 [Abstract] [Full Text]
- Nagaya, N., Uematsu, M., Kojima, M., Date, Y., Nakazato, M., Okumura, H., Hosoda, H., Shimizu, W., Yamagishi, M., Oya, H., Koh, H., Yutani, C., Kangawa, K. (2001). Elevated Circulating Level of Ghrelin in Cachexia Associated With Chronic Heart Failure: Relationships Between Ghrelin and Anabolic/Catabolic Factors. *Circulation* 104: 2034-2038 [Abstract] [Full Text]
- Coats, A. J S (2001). HEART FAILURE: What causes the symptoms of heart failure?. *Heart* 86: 574-578 [Full Text]
- Smit, J. W. A., Janssen, Y. J. H., Lamb, H. J., van der Wall, E. E., Stokkel, M. P. M., Viergever, E., Biermasz, N. R., Bax, J. J., Vliegen, H. W., de Roos, A., Romijn, J. A., Roelfsema, F. (2001). Six Months of Recombinant Human GH Therapy in Patients with Ischemic Cardiac Failure Does Not Influence Left Ventricular Function and Mass. *J Clin Endocrinol Metab* 86: 4638-4643 [Abstract] [Full Text]
- Nagaya, N., Uematsu, M., Kojima, M., Ikeda, Y., Yoshihara, F., Shimizu, W., Hosoda, H., Hirota, Y., Ishida, H., Mori, H., Kangawa, K. (2001). Chronic Administration of Ghrelin Improves Left Ventricular Dysfunction and Attenuates Development of Cardiac Cachexia in Rats With Heart Failure. *Circulation* 104: 1430-1435 [Abstract] [Full Text]
- HEINDL, S., LEHNERT, M., CRIEE, C.-P., HASENFUSS, G., ANDREAS, S. (2001). Marked Sympathetic Activation in Patients with Chronic Respiratory Failure. *Am J Respir Crit Care Med* 164: 597-601 [Abstract] [Full Text]
- Akner, G., Cederholm, T. (2001). Treatment of protein-energy malnutrition in chronic nonmalignant disorders. *Am. J. Clin. Nutr.* 74: 6-24 [Abstract] [Full Text]
- Bolger, A., Doehner, W., Anker, S. D (2001). Insulin-like growth factor-I can be helpful towards end of life. *BMJ* 322: 674b-674 [Full Text]
- Rauchhaus, M., Doehner, W., Francis, D. P., Davos, C., Kemp, M., Liebenthal, C., Niebauer, J., Hooper, J., Volk, H.-D., Coats, A. J. S.,

Anker, S. D. (2000). Plasma Cytokine Parameters and Mortality in Patients With Chronic Heart Failure. *Circulation* 102: 3060-3067 [Abstract] [Full Text]

- Moriyama, Y., Yasue, H., Yoshimura, M., Mizuno, Y., Nishiyama, K., Tsunoda, R., Kawano, H., Kugiyama, K., Ogawa, H., Saito, Y., Nakao, K. (2000). The Plasma Levels of Dehydroepiandrosterone Sulfate Are Decreased in Patients with Chronic Heart Failure in Proportion to the Severity. *J Clin Endocrinol Metab* 85: 1834-1840 [Abstract] [Full Text]
- Osterziel, K. J., Blum, W. F., Strohm, O., Dietz, R. (2000). The Severity of Chronic Heart Failure due to Coronary Artery Disease Predicts the Endocrine Effects of Short-Term Growth Hormone Administration. *J Clin Endocrinol Metab* 85: 1533-1539 [Abstract] [Full Text]
- Bozkurt, B. (2000). Activation of cytokines as a mechanism of disease progression in heart failure. *Ann Rheum Dis* 59: i90-93 [Full Text]
- Pugh, P.J., English, K.M., Jones, T.H., Channer, K.S. (2000). Testosterone: a natural tonic for the failing heart?. *QJ Med* 93: 689-694 [Full Text]
- IONESCU, A. A., NIXON, L. S., EVANS, W. D., STONE, M. D., LEWIS-JENKINS, V., CHATHAM, K., SHALE, D. J. (2000). Bone Density, Body Composition, and Inflammatory Status in Cystic Fibrosis. *Am J Respir Crit Care Med* 162: 789-794 [Abstract] [Full Text]
- Anker, S. D., Coats, A. J. S. (1999). Cardiac Cachexia: A Syndrome With Impaired Survival and Immune and Neuroendocrine Activation. *Chest* 115: 836-847 [Abstract] [Full Text]
- Murdoch, D R, Rooney, E, Dargie, H J, Shapiro, D, Morton, J J, McMurray, J J V (1999). Inappropriately low plasma leptin concentration in the cachexia associated with chronic heart failure. *Heart* 82: 352-356 [Abstract] [Full Text]
- Coats, A. J. S. (1999). Exercise Training for Heart Failure : Coming of Age. *Circulation* 99: 1138-1140 [Full Text]
- SWYNGHEDAUW, B. (1999). Molecular Mechanisms of Myocardial Remodeling. *Physiol. Rev* 79: 215-262 [Abstract] [Full Text]
- Dreifuss, P., Anker, S. D., Coats, A. J.S. (1998). Growth Hormone in Chronic Heart Failure • Response. *Circulation* 97: 1650-1651 [Full Text]
- Dreifuss, P., Anker, S. D., Coats, A. J.S. (1998). Growth Hormone in Chronic Heart Failure • Response. *Circulation* 97: 1650-1651 [Full Text]
- Bristow, M. R. (1998). Tumor Necrosis Factor-{alpha} and Cardiomyopathy. *Circulation* 97: 1340-1341 [Full Text]

CIRCULATION

The New England Journal of Medicine

ORIGINAL ARTICLE

◄ Previous Volume 323:236-241 July 26, 1990 Number 4 Next ►

Elevated circulating levels of tumor necrosis factor in severe chronic heart failure

B Levine, J Kalman, L Mayer, HM Fillit, and M Packer

Abstract

BACKGROUND AND METHODS. Although cachexia often accompanies advanced heart failure, little is known about the causes of the cachectic state. To assess the potential role of tumor necrosis factor in the pathogenesis of cardiac cachexia, we measured serum levels of the factor in 33 patients with chronic heart failure, 33 age-matched healthy controls, and 9 patients with chronic renal failure. RESULTS. Mean (+/- SEM) serum levels of tumor necrosis factor were higher in the patients with heart failure (115 +/- 25 U per milliliter) than in the healthy controls (9 +/- 3 U per milliliter; P less than 0.001). Nineteen of the patients with chronic heart failure had serum levels of tumor necrosis factor greater than or equal to 39 U per milliliter (greater than 2 SD above the mean value for the control group), whereas the remaining 14 patients had serum levels of tumor necrosis factor below this level. The patients with high levels of tumor necrosis factor were more cachectic than those with low levels (82 +/- 3 vs. 95 +/- 6 percent of ideal body w ight, respectively; P less than 0.05) and had more advanced heart failure, as evidenced by th ir higher values for plasma renin activity (2.92 +/- 0.53 vs. 1.06 +/- 0.53 ng per liter per second [10.5 +/- 1.9 vs. 3.8 +/- 1.9 ng per milliliter per hour]; P less than 0.01) and lower serum sodium concentration (135 +/- 1 vs. 138 +/- 1 mmol per liter; P less than 0.05). The group with high l vels of tumor necrosis factor also had lower hemoglobin levels (7.82 +/- 0.2 vs. 8.69 +/- 0.4 mmol per liter [12.6 +/- 0.4 vs. 14.0 +/- 0.6 g per deciliter]) and higher values for blood urea nitrogen (19.5 +/- 2.2 vs. 12.5 +/- 1.8 mmol per liter) than the group with low levels of tumor n crosis factor (P less than 0.05 for both). The high levels of tumor necrosis factor were not due solely to decreased renal clearance, however, since the levels in the patients with heart failure were considerably higher than those in the nine patients with chronic renal failure (115 +/- 25 vs. 45 +/- 25 U per milliliter; P less than 0.05). CONCLUSIONS. These findings indicate that circulating levels of tumor necrosis factor are increased in cachectic patients with chronic heart failure and that this elevation is associated with the marked activation of the renin-angiotensin system seen in patients with end-stage cardiac disease.

Sourc Information

Department of Medicine, Mount Sinai School of Medicine, City University of New York, New York 10029.

This article has been cited by other articles:

- Amadou, A., Nawrocki, A., Best-Belpomme, M., Pavoine, C., Pecker, F. (2002). Arachidonic acid mediates dual effect of TNF-alpha on Ca2+ transients and contraction of adult rat cardiomyocytes. *Am. J. Physiol.* 282: C1339-1347 [Abstract] [Full Text]
- Mabuchi, N., Tsutamoto, T., Wada, A., Ohnishi, M., Maeda, K., Hayashi, M., Kinoshita, M. (2002). Relationship Between Interleukin-6 Production in the Lungs and Pulmonary Vascular Resistance in Patients With Congestive Heart Failure*. *Chest* 121: 1195-1202 [Abstract] [Full Text]
- Taegtmeyer, H., McNulty, P., Young, M. E. (2002). Adaptation and Maladaptation of the Heart in Diabetes: Part I: General Concepts. *Circulation* 105: 1727-1733 [Full Text]
- Colombo, P. C., Ashton, A. W., Celaj, S., Talreja, A., Banchs, J. E., Dubois, N. B., Marinaccio, M., Malla, S., Lachmann, J., Ware, J. A., Le Jemtel, T. H. (2002). Biopsy coupled to quantitative immunofluorescence: a new method to study the human vascular endothelium. *J. Appl. Physiol.* 92: 1331-1338 [Abstract] [Full Text]
- (1990). A POSSIBLE EXPLANATION FOR CARDIAC CACHEXIA. *Journal Watch General Medicine* 1990: 6-6 [Full Text]
- Heger, J., Godecke, A., Flogel, U., Merx, M. W., Molojavyi, A., Kuhn-Velten, W. N., Schrader, J. (2002). Cardiac-Specific Overexpression of Inducible Nitric Oxide Synthase Does Not Result in Severe Cardiac Dysfunction. *Circulation Research* 90: 93-99 [Abstract] [Full Text]
- Densem, C G, Hutchinson, I V, Yonan, N, Brooks, N H (2002). Tumour necrosis factor {alpha} gene polymorphism: a predisposing factor to non-ischaemic myocardial dysfunction?. *Heart* 87: 153-155 [Abstract] [Full Text].
- Elkind, M. S., Cheng, J., Boden-Albala, B., Rundek, T., Thomas, J., Chen, H., Rabbani, L. E., Sacco, R. L., Thrift, A. G. (2002). Tumor Necrosis Factor Receptor Levels Are Associated With Carotid Atherosclerosis * Editorial Comment. *Stroke* 33: 31-38 [Abstract] [Full Text]
- Iversen, P. O., Woldbaek, P. R., Tonnessen, T., Christensen, G. (2002). Decreased hematopoiesis in bone marrow of mice with congestive heart failure. *Am. J. Physiol.* 282: R166-172 [Abstract] [Full Text]
- Fichtlscherer, S., Rossig, L., Breuer, S., Vasa, M., Dimmeler, S., Zeiher, A. M. (2001). Tumor Necrosis Factor Antagonism With Etanercept Improves Systemic Endothelial Vasoreactivity in Patients With Advanced Heart Failure. *Circulation* 104: 3023-3025 [Abstract] [Full Text]
- Nagaya, N., Uematsu, M., Kojima, M., Date, Y., Nakazato, M., Okumura, H., Hosoda, H., Shimizu, W., Yamagishi, M., Oya, H., Koh, H., Yutani, C., Kangawa, K. (2001). Elevated Circulating Level of Ghrelin in Cachexia Associated With Chronic Heart Failure: Relationships Between Ghrelin and Anabolic/Catabolic Factors. *Circulation* 104: 2034-2038 [Abstract] [Full Text]
- Nagaya, N., Uematsu, M., Kojima, M., Ikeda, Y., Yoshihara, F., Shimizu, W., Hosoda, H., Hirota, Y., Ishida, H., Mori, H., Kangawa, K.